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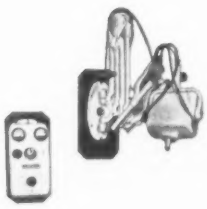

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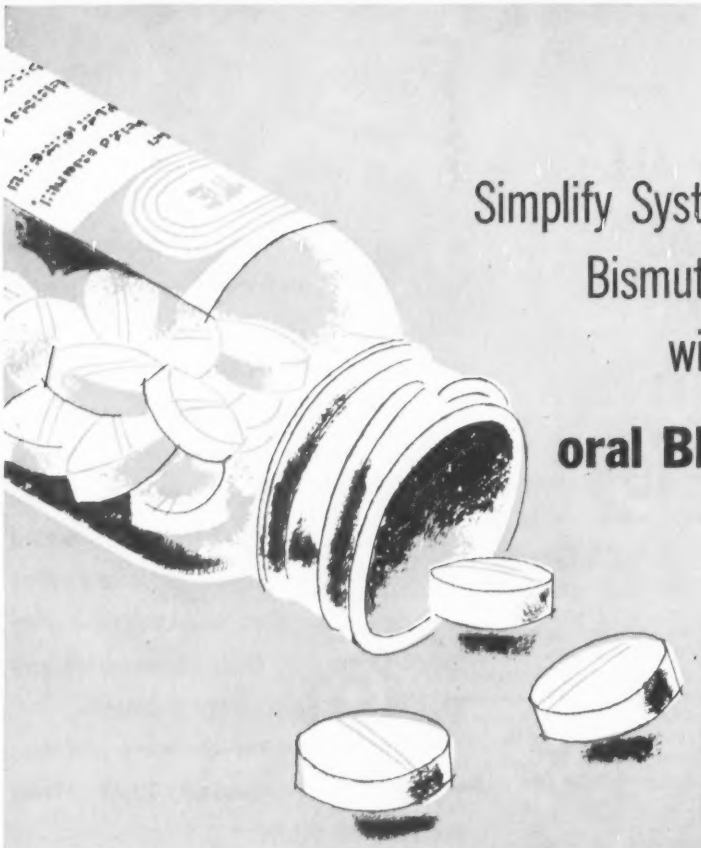

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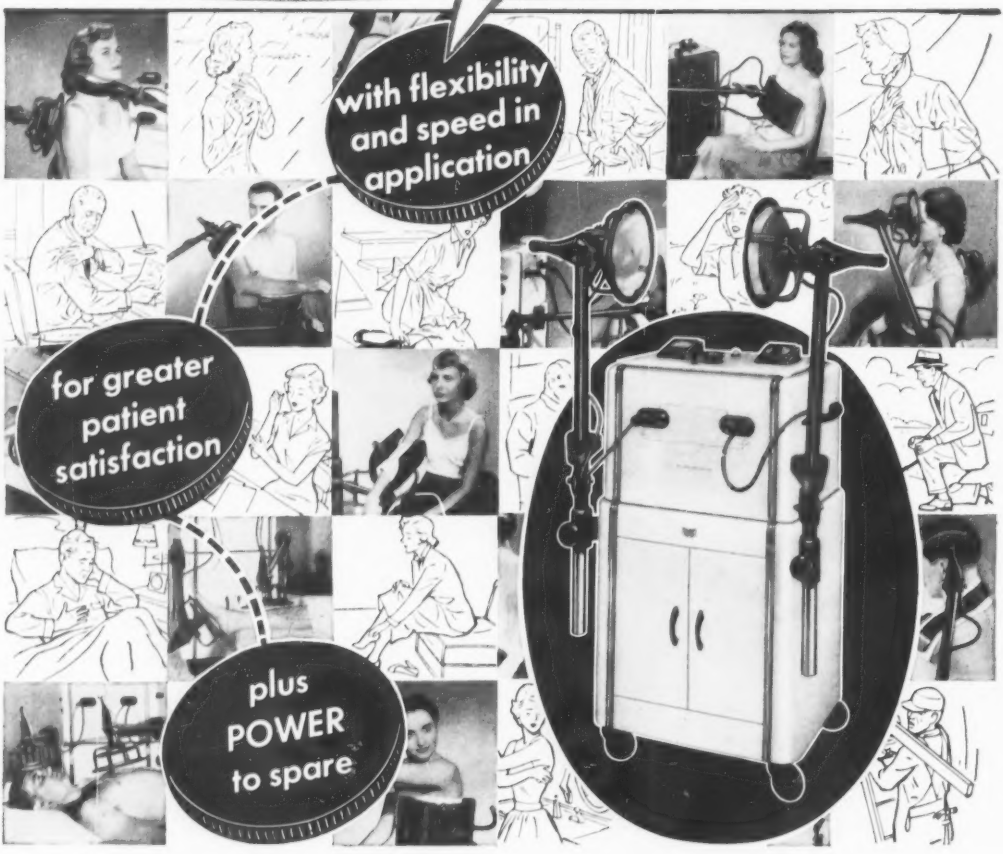

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1. Sulzberger, M.B. *et al.*: *J.A.M.A.* **151**: 468, Feb. 7, 1953
2. Smith, C. C.: *A.M.A. Arch. Dermat. & Syph.* **68**: 50, July, 1953

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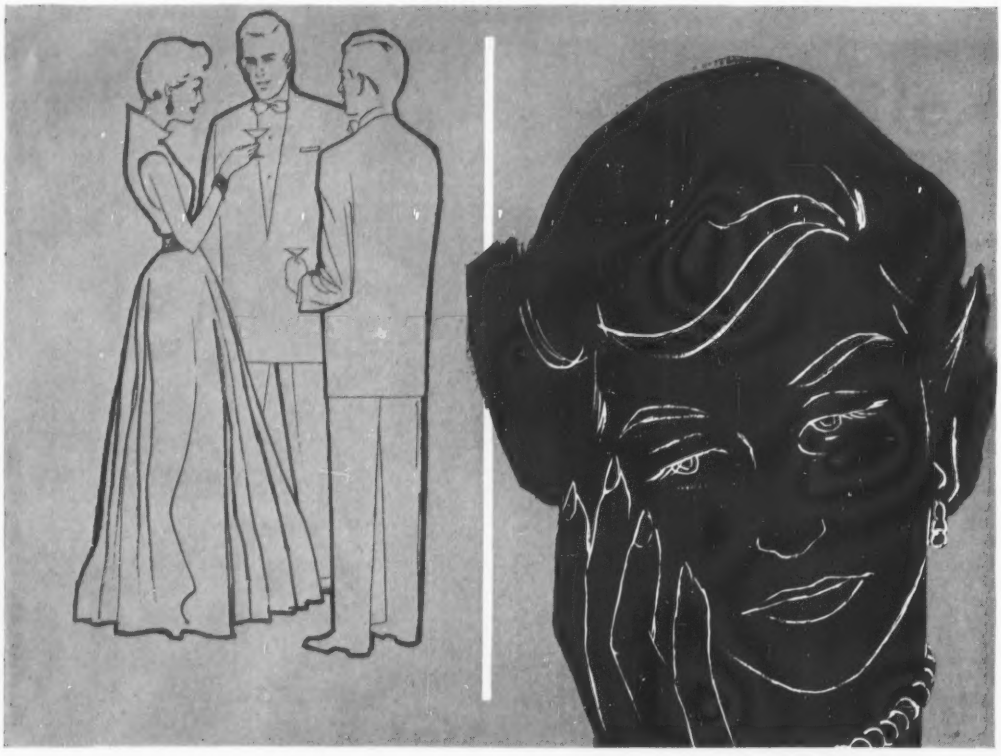

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References

(1) Kirby, W. M. M.; Waddington, W. S., & Doornink, G. M.: Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, p. 285. (2) Finland, M., & Haight, T. H.: *Arch. Int. Med.* 91: 143, 1953.

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VOLUME 70 OCTOBER 1954 NUMBER 4

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TREATMENT OF BENIGN PIGMENTED MOLES

CAPTAIN GORDON H. EKBLAD (MC), U.S.N.

THE TREATMENT of pigmented moles has long been a controversial subject. This controversy extends up to, but unfortunately does not end with, the opinions of our accepted authorities on the subject of pigmented moles and melanomas. Obviously our opinions must be influenced by cancer centers treating large numbers of melanomas, and by groups of physicians treating large numbers of pigmented moles. Since authorities in these fields are by no manner in accord as to the proper handling of pigmented moles, the issue must of necessity remain befuddled to the average practitioner.

Driver and MacVicar in 1943 probably reviewed the literature more extensively than others, but their paper was concerned primarily with the treatment of melanomas. This paper attempts to bring together for the first time (to the author's knowledge) the viewpoints and opinions from all possible sides, as expressed by a large number of authorities, on the treatment of pigmented moles. Thus, the reader has the opportunity to weigh these opinions as expressed by various authorities, and form his own conclusions.

OBJECT OF ARTICLE

The object of this paper is to clarify the treatment of clinically benign moles. Since the subject of melanomas is so intricately tied up with the proper management of moles, a number of statements are included pertaining to melanomas. The subject of treatment of melanomas, suspected melanomas, or suspicious nevi, however, is not dealt with.

Pertinent statements from 30 articles or texts are quoted verbatim. These include opinions of dermatologists, histopathologists, roentgenologists, and surgeons. Since these various statements make up the very meat of the issue in question, they are included in the body of this paper. Reference numbers pertain not to a particular article as such, but to a particular sentence or sentences or paragraph, with which the reference number is associated. It would be impossible to clearly discuss such a controversial subject without some anchor about which to swing, and my own opinions are used as such.

DEFINITIONS

The terms mole and nevus are herein used synonymously with the term nevus pigmentosus, to designate any lesion containing nevus (melanocyte) cells.

The term melanoma is used synonymously with the term malignant melanoma, to designate any lesion containing malignant nevus or melanomatous cells.

Department of Dermatology, U. S. Naval Hospital, Corona, Calif.

The opinions expressed are those of the author, and do not necessarily reflect the views of the Medical Department of the Navy or of the Navy Department.

For the histopathological terms (1) junctional nevi, (2) intradermal nevi, (3) compound nevi, (4) blue nevi, and (5) juvenile melanoma, the reader is referred to standard texts, or to pertinent articles referred to in this paper.*

Very briefly, (1) a junctional nevus is one with nevus cells at the epidermodermal junction; (2) an intradermal nevus consists of nevus cells confined to the dermis; (3) a compound nevus consists of both junctional cells and intradermal nevus cells; (4) blue nevi are not concerned with in this article, in view of the rarity of their becoming malignant, and because of the fact that there is only one generally used method of treatment, surgical excision; (5) juvenile melanoma refers to nevi in prepubertal children (also recognizable as such in adults) which show histopathological pictures difficult or impossible to distinguish from true melanoma, but which do not behave as such; this lesion is left to other articles for further clarification and discussion.†

In regard to compound nevi and intradermal nevi, it might be stated that many general pathologists and dermato histopathologists feel that if serial sections were run through the entire lesion of an intradermal nevus, probably most sections would show at least one junctional element and as such could be classified as a compound nevus. However, it must be assumed from percentages quoted for the occurrence of compound nevi that intradermal nevi showing only occasional occurrence of a junctional element are generally considered as intradermal nevi. There has never been any clarification as to just where this dividing line should be drawn. It must also be fair to assume from all available quotes and figures which ignore this factor in discussing intradermal nevi that this very occasional junctional element in an otherwise intradermal nevus does not effect the results of treatment of these lesions.

GENERAL STATEMENTS

The annual incidence of melanocarcinoma in the general population is 1.8 per 100,000 (0.0018%).[19]

The average individual has 15 to 20 pigmented moles.‡ The annual incidence then, of melanoma per mole is 1.8 per 1,500,000 (0.00012%; 1.8 per 100,000 × 15, employing the more conservative figure of 15 moles per person).

Many figures on the percentages of melanomas as compared to epitheliomas, as taken from the files of larger cancer centers, would tend to indicate a larger percentage of melanomas than the above figures. This is undoubtedly due to the fact that the more serious malignant tumors (i. e., melanomas) tend to gravitate to those centers.

It would take the physicians of the United States, if they neglected all other work and did nothing but excise moles, 2.3 years to accomplish this task. (This assumes 211,000 physicians, a 300-working-day year, eight-hour day, 155,000,000 people, and one-half hour per mole to adequately prepare and excise and decently close, and 15 moles per person).

There would obviously be no problem if there were more melanomas and fewer moles—all the moles should be removed. However, if the annual rate of malignancy

* References 2, 3, 4, 12, 16, 17, 23, 27, and 28.

† References 2, 3, 12, 16, 23, and 27.

‡ References 1*a*, 18*a*, and 19.

is only one per million moles, this is impractical, to say the least. The problem is, which moles to treat and how. Most moles obviously need not be treated.

The reasons are obvious in those moles treated for cosmetic reasons.

Prophylactically, it is probably good practice to remove moles on the soles, palms, pulp of fingers and toes, and on the genitals, and those moles subject to repeated trauma.§ In view of the small number which become malignant, it is probably equally poor practice to unnecessarily alarm patients with such lesions.

While this paper is concerned only with the treatment of clinically benign moles, it might be added here that, obviously, moles showing any suspicious changes should be excised and histologically examined.

When a clinically benign lesion is treated by excision, adequate and not radical excision is sufficient. Adequate excision, as distinguished from radical excision, is an excision which leaves a margin of about 2 mm. of normal skin. As long as the histopathological sections show a benign lesion, and the excision extends beyond the margins of the nevus cells (in width and depth), there can be no sound reason for a radical excision. Benign cells are not potentially malignant in vitro.[22d]

The junction type nevus, and not the intradermal nevus, is the potentially malignant lesion.‖

It is not possible, clinically, to always differentiate the various types of nevi; the junctional from the intradermal, the potentially dangerous from the always benign type.¶

It is not always possible, clinically, to differentiate the benign nevus from the malignant melanoma.#

There is a greater margin of safety in treating nevi prior to puberty, than after puberty.*

There has never been a histologically proved benign nevus which has become malignant. It would seem intuitively that such a transformation does take place, but there is as yet no histological proof that it does so.†

TREATMENT OF INTRADERMAL-TYPE NEVI

Clinically, the intradermal nevus is usually an elevated, smooth, papular lesion. It may, however, be verrucous or pedunculated. It may be flesh-colored to fairly heavily pigmented. It may or may not contain hairs.‡

About 12% of this clinical type will prove histologically to be compound nevi.[3c]

Method 1.—Excision may be the preferred method in those locations where better cosmetic results can be expected than with other methods. The advantages are removal of all nevus cells, and histological examination. The disadvantages are more expense to the patient and objectionable scars in certain locations; the patient may not submit to surgery for a minor lesion which he wishes removed for cosmetic reasons.

§ References *2c*, *15b*, *20a*, *20b*, and *28c*.
‖ References *3a*, *3b*, *10a*, *12d*, *17b*, *28a*, and *28b*.
¶ References *5a*, *10b*, *12a*, *21*, and *26*.
# References *3d* and *22a*.
* References *8*, *12c*, *20d*, *23*, and *27*.
† References *2b*, *5b*, *22b*, *28d*, and *30*.
‡ References *2a*, *5a*, *12b*, and *15a*.

Method II.—The majority of this type of nevi are probably most easily handled by shaving off flush with the skin for biopsy. The base is then lightly desiccated, including the peripheral margins. If the biopsy sections show an intradermal nevus, the remaining intradermal cells need not be treated. Where the biopsy sections show a compound nevus, the junctional cells will have been removed, providing the desiccation has been carried wide enough to remove superficially compounded elements at the periphery, and the remaining intradermal cells need not be treated. Advantages are ease of treatment, histological examination, little expense to the patient, and good cosmetic results.

Method III.—Carbon dioxide, trichloroacetic acid, electrolysis, and electrodesiccation, are frequently used methods of treatment. Advantages are ease of treatment, little expense to the patient, and good cosmetic results. Disadvantages are lack of biopsy and the strict requirement of adequate experience to judge properly which lesions can be safely treated in these manners.§

TREATMENT OF COMPOUND-TYPE NEVI

Strictly speaking, it is probably not clinically possible to judge whether these nevi will be intradermal, compound, or junctional types. However, for sake of classifying, the compound type nevi may be considered to be slightly raised, round to oval, of varying sizes, with or without hairs, moderately to deeply pigmented lesions (in other words, anything falling between the typical papular intradermal type, and the typical small flat junctional type).‖

Method I.—Excision is the method of choice where good cosmetic results can be expected.

Method II.—Many nevi of this type are not sufficiently elevated to allow adequate biopsy by this method (as used with intradermal nevi). Where biopsy can be done, and where it shows a junctional type nevus, the area should be excised or destroyed (as by electrocoagulation) deeply enough to insure destruction of any remaining nevus cells. The latter may give undesirable scars.

Method III.—Without biopsy, it is probably impossible to judge clinically, with reasonable accuracy, the lesions of this type which can be safely treated by superficial methods with only cosmetic results in mind, and without destruction of all nevus cells.

References.—It is usually difficult to tell from most articles when they are referring specifically to this type nevus, and the reader is referred to references listed under intradermal and junction type nevi.

TREATMENT OF JUNCTION-TYPE NEVI

The junction type nevus is generally a small (usually 2 to 5 mm.), smooth, flat to slightly raised, usually without hairs, brown to deeply pigmented, lesion.¶

Any nevi occurring on the palms, soles, pulps of fingers or toes, or scotum, can, for all practical purposes, be considered junctional.#

§ References 1*b*, 2*b*, 3*b*, 4*a*, 4*b*, 4*c*, 4*d*, 5*c*, 6*a*, 6*b*, 10*a*, 10*c*, 14, 17*a*, 17*b*, 20*c*, 22*a*, 22*c*, 24*a*, 25, 28*b*, and 29.

‖ References 5*a*, 12*a*, and 21.

¶ References 5*a*, 7*a*, 10*b*, 12*c*, and 15*a*.

References 2*a*, 2*c*, and 28*c*.

Method I.—Inasmuch as these are the acknowledged dangerous type of nevi, Method I (excision) is the method of choice.

Method II.—This method (as used in intradermal nevi) does not lend itself to the treatment of this type of nevi, as all nevus cells should be destroyed. Admittedly, these small lesions can be easily and adequately (adequately, in this type nevus, means all nevus cells destroyed) treated by means of electrocoagulation, carbon dioxide, or trichloracetic acid. The disadvantages, aside from the necessary prerequisite of knowledge of the proper use of these modalities, is lack of biopsy and a slightly depressed scar. In this vein, it must also be admitted that while biopsy of all lesions is the ideal goal, it is not always feasible. The additional expense of histological specimens will prevent many patients from having these lesions treated. Many patients will balk at excision, which to them may seem a comparatively major procedure for a minor lesion. If it is considered good prophylactic measure to destroy this type of lesion, and if insistence on biopsy will mitigate against the great majority of these lesions ever being treated, then it should be good practice to destroy these lesions by any adequate method, even though it may not be the method of choice. Inadequate treatment, of course, is to be condemned. This argument does not apply to clinically suspicious lesions, where histopathological study should always be done.

Method III.—Any superficial method of treatment which does not destroy all nevus cells should never be used in this type of lesion.*

TREATMENT OF LARGE NEVI

These nevi come mostly within the scope of plastic surgeons. Excision by decrements, if the lesion is not of the junction type, is apparently the method of choice where applicable. If the lesion is of the junctional type, this procedure should be done prior to puberty. Excision in toto with repair by plastic flap gives less satisfactory cosmetic results.†

SUMMARY

Conservative treatment of intradermal nevi is safe if biopsy is done.

Treatment of junction-type nevi should insure removal or destruction of all nevus cells.

The clinically compound-type nevi fall in between the intradermal and the junctional type nevi, and good clinical judgment is imperative in their treatment.

The junction-type nevus, and not the intradermal nevus, is the potentially malignant lesion.

There has never been a histologically proved benign nevus which has become malignant. It would seem intuitively that such a transformation does take place, but there is as yet no histological proof that it does so.

* References *1b*, *4a*, *4b*, *4c*, *5c*, *6a*, *6b*, *7b*, *9a*, *10d*, *17a*, *20c*, *22a*, *22c*, *22d*, *24b*, *25*, *28a* and *29*.
† References *8*, 11, and *20d*.

REFERENCES

The following references and the pertinent quotations formed the basis of my research.

1. Adair, F. E.: Treatment of Melanoma, Surg. Gynec. & Obstet. **62** (No. 2A): 406-409 (Jan.) 1936.

(*a*) The average person has about 20 pigmented moles, if he has reached the age of 40.

(*b*) I am convinced by the study of our 400 cases that the electric needle applied with good intent but without sufficient accuracy, is the one trauma responsible for as much wild growth as any other form of injury. It is appalling that in 38 instances [of melanoma], or nearly 10%, electrodesiccation of the lesion was employed.

2. Allen, A. C.: A Reorientation on the Histogenesis and Clinical Significance of Cutaneous Nevi and Melanomas, Cancer **2**:28-56 (Jan.) 1949.

(*a*) The [intradermal] nevus may occur in the skin of any part of the body excepting, for all practical purposes, the scrotum, the palms, the soles, and the pulps of the fingers and toes. Clinically it may vary considerably in appearance from pink to various shades of brown, from a flat macule to a papillary warty growth. The intradermal nevus may or may not contain hairs; on the other hand, when a pigmented nevus contains hairs, it is extremely likely to be of this variety.

(*b*) It is currently assumed that local caustic or coagulative therapy unquestionably flares up dormant nevi. Actually, as indicated, there is good reason to believe that such handling is really innocuous if the nevi are the simple intradermal or the blue nevi uncomplicated by the junctional type. However, even in the case of the junctional nevi, there is lacking the properly required statistical and histological proof that trauma transforms a junctional nevus into a malignant melanoma, even though intuitive support of such a thesis is understandable.

(*c*) Because it may be assumed that nevi of the scrotum and of the palmar and plantar aspects of the extremities are junctional nevi, it would seem wise to remove such nevi prophylactically, preferably prior to puberty.

3. Allen, A. C., and Spitz, S.: Malignant Melanoma: A Clinicopathological Analysis of the Criteria for Diagnosis and Prognosis, Cancer **6**:1-45 (Jan.) 1953.

(*a*) Unlike the intradermal nevi, some of the quiescent junctional nevi—luckily only a small proportion—do become active and do eventuate in melanocarcinomas. To date, it is impossible to know which particular ones will undergo malignant changes.

(*b*) It appears fairly certain that no amount of trauma to the intradermal nevus will convert it into a malignant lesion.

(*c*) The junctional component occurs in about 98 per cent of the intradermal nevi of children, and in about 12 per cent of those of adults.

(*d*) We have seen three cases in which, despite widespread metastasis, the primary cutaneous melanoma was not discovered until autopsy when the prosector took sections of what seemingly were commonplace moles clinically, but which were actually superficial melanomas.

Of the 934 patients studied, 68.3 per cent who survived five years or longer were treated merely by local excision of the primary tumor.

4. Becker, S. W.: Diagnosis and Treatment of Pigmented Nevi, Arch. Dermat. & Syph. **60**:44-65 (July) 1949.

(*a*) The *sine qua non* for treatment is to determine whether the lesion is clinically a pigmented nevus and not lentigo maligna or melanoma.

(*b*) With the use of local anesthesia, small [macular] lesions are cauterized with a major electrocautery deeply enough to destroy the epidermis and adjacent cells but not so deep as to cause appreciable scarring. There is no reason that solid carbon dioxide or electrocoagulation could not be used by one who is experienced in their use.

(*c*) Large macular nevi are treated by fulguration, with local anesthesia.

(*d*) Papular nevi on the face or neck are snipped off with scissors for biopsy. The area is then cauterized with the electrocautery to such a depth that when the wound is healed the scar will be flush with the epidermal surface. No effort is made to destroy all dermal nevus cells, since, in my experience, they are harmless. Small papular pilose nevi may be treated by epilation of hairs, followed by biopsy, and then cauterization of the mole at the first visit. Removal of hair with the epilating needle without subsequent immediate treatment of the nevus is not considered safe. Treatment of peduncu-

lated nevus is simple and consists merely of clipping off the lesion at the base and cauterizing the base. This procedure removes the entire lesion, with the possible exception of a few deep nevus cells, which, in my experience, are harmless. A biopsy is made of all such specimens. The results of treatment of the common mole, which is papular or pedunculated, are excellent. In some instances, in which the brown color persists after initial cautery, a second treatment is given.

5. Becker, S. W.: Dermatological Investigations of Melanin Pigmentation, in the Biology of Melanomas, New York, New York Academy of Sciences, 1948.

(*a*) Clinically, it is impossible to differentiate the different varieties; microscopic examination is necessary.

(*b*) In cases [of melanomas] where the patient gives a history of having had a "mole" removed, it has been possible to obtain sections of the specimen so removed in only a few instances. In these, upon examination, the process was malignant from the start.

(*c*) Conservative therapy of nevi, as practiced by the dermatologist, can be safe only if all lesions are biopsied.

6. Butterworth, T., and Klauder, J. V.: Malignant Melanomas Arising in Moles, J. A. M. A. **102**:739-745 (March 10) 1934.

(*a*) Malignant melanomas may arise in either flat or elevated moles. In our series [fifty cases] the moles were recorded in the histories as macular, eleven cases; nodular, six cases; warty, two cases; pedunculated, two cases. In twenty-nine cases the type of mole was not mentioned. In twenty-seven cases, distinct mention was made of the color of the antecedent mole as follows: black, five cases; black and hairy, one case; brown-black, one case; dark brown, five cases; brown, fourteen cases; flesh colored, one case. In the remaining twenty-three cases the color of the antecedent mole was not recorded.

(*b*) It is not possible to prove that a malignant condition appearing after trauma is not a coincidence. It is reasonable to ascribe, however, an etiologic role to trauma in such reported cases and in our series.

7. Couperus, M., and Rucker, R. C.: Early Diagnosis of Malignant Melanoma of the Skin, California Med. **78**:21-24 (Jan.) 1953.

(*a*) Nearly all junction nevi are between 2 and 5 mm. in size.

(*b*) Although it is certainly possible to destroy a junction nevus by various methods, including electrocoagulation, all methods except adequate surgical excision should be condemned. Only with surgical excision is there absolute certainty that the lesion has been completely eradicated, and only by this method is a specimen obtained for histopathologic study.

8. Cronin, T. D.: Extensive Pigmented Nevi on Hairbearing Areas, Plast. & Reconst. Surg. **11**:94-106 (Feb.) 1953.

This method [Note: combination of (1) multiple partial excisions, (2) electrocoagulation of the pigment bearing portion of the skin in the hair-bearing areas deeply enough to remove the pigment, but not deep enough to destroy the hair follicles, and (3) removal of the nevus as a thick split-skin graft] can be used without fear of causing malignant change on intradermal nevi at any age, but in the case of junctional or compound nevi, its use should be restricted to children below the age of puberty.

9. Driver, J. R., and MacVicar, D. N.: Cutaneous Melanomas: A Clinical Study of 60 Cases, J. A. M. A. **121**:413-420 (Feb. 6) 1943.

Of a series of 60 patients with melanomas, a group of 25 patients seen in hospital surgical practice presented themselves for treatment comparatively late, with relatively advanced malignant growths and a large percentage showing metastatic involvement. Only 2 patients are known to be alive more than five years later. The mortality rate was 92 per cent.

Of the other group of 35 patients seen in dermatologic practice 17, or 48.6 per cent survived from seven to eighteen years. As a group these patients were seen comparatively early in their disease and the great majority were free of metastatic dissemination when they were first treated.

(*a*) The results obtained indicate that the only hope of reducing the high mortality rate in cutaneous melanoma lies in early diagnosis and thorough destruction of the primary lesion before dissemination takes place, either by electrocauterization (not electrolysis) or by radical scalpel excision.

10. Eller, J. J., and Eller, W. D.: Tumors of the Skin: Benign and Malignant, Ed. 2, Philadelphia, Lea & Febiger, 1951.

(*a*) Intradermal nevus—rarely, if ever, undergoes malignant changes.

(*b*) As a rule the junction nevus is a slightly elevated, smooth, pea-sized, non-hairy lesion, deep brown to black in color. However, it may be at times difficult to differentiate clinically from other types of nevi and other neoplasms.

(*c*) Small pigmented nevi can be excised and the edges of the defect closed with very fine skin sutures, often with excellent cosmetic results. Surgical excision is considered by many to be the safest and the best method for the eradication of pigmented nevi because its allows the removal of the entire lesion with some of the adjacent tissue. However, most patients refuse to submit to a surgical operation for a minor lesion which they wish treated for cosmetic reasons. Electrolysis may give excellent cosmetic results. Applications of solid carbon dioxide may also be effective, but is employed with greater facility in treating larger lesions. Some of the superficial non-hairy benign pigmented nevi, the size of a lentil or smaller, have been treated with good results by applications of trichloracetic acid. For treatment of small hairy pigmented nevi it is good practice first to destroy the hair roots by electrolysis. This frequently causes involution of the entire lesion, but if additional treatment is necessary, any of the aforementioned methods, such as solid carbon dioxide or trichloracetic applications, may be used. However, the electrolytic removal of the hairs from a hairy nevus without complete treatment of the entire lesion is not considered safe by many dermatologists.

(*d*) The treatment of junction type nevus should be complete and should include normal tissue beyond the periphery and depth of the nevus tissue.

11. Farris, J. M.: Origin and Treatment of Malignant Melanoma, California Med. **78**:110-116 (Feb.) 1953.

Excision and split thickness graft—of the large hairy nevi—give a cosmetically unsatisfactory result in most instances. A preferable alternative is stage excision in decrements of thirds, fourths, or fifths depending upon the size of the tumor. There need be little fear of inciting malignancy through operation on this lesion.

12. Lever, W.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

(*a*) It is not always possible to predict from the clinical appearance whether the nevus is of the intradermal type or the junction type.

(*b*) As a rule, the intradermal nevus is a circumscribed, smooth or slightly verrucous elevation which may or may not contain a number of hairs and varies in color from normal skin to dark brown.

(*c*) The junction nevus is a relatively flat or slightly raised, smooth, pigmented mark that is devoid of hairs. Its color is light brown or brownish-black, rarely slate-blue or bluish-black.

(*d*) Junction nevi are potentially malignant because they are active nevi, not resting nevi as intradermal nevi. They possess the ability for further growth.

(*e*) Malignant melanoma is rare before puberty and when it occurs it is usually clinically benign.

13. Macdonald, E. J.: Malignant Melanoma in Connecticut, in The Biology of Melanomas, New York, New York Academy of Sciences, 1948.

Malignant melanoma has accounted for .93 per cent of the total cancer in Connecticut for the past twelve years. Every effort has been made to obtain the actual incidence of cancer in this state.

For malignant melanoma, the annual average incidence rate, which is the relative number of cases diagnosed in a given year, is 1.8 per 100,000 population.

14. MacKee, N., and Cipollaro, A. C.: X-Rays and Radium in Treatment of Diseases of the Skin, Ed. 4, Philadelphia, Lea & Febiger, 1947.

In nevus pilosus et pigmentosus, there is a difference of opinion as to whether the hair should be removed with radiation or with electrolysis. Many dermatologists aver that the electrolytic needle should never be inserted into a mole or any kind of pigmented nevus. Others claim that there is more danger associated with irradiation than with electrolysis. It is our opinion that the "needle" method is safe and that irradiation is dangerous. We never employ irradiation for this purpose.

15. Montgomery, H.: Benign and Malignant Moles (Nevi): Their Differentiation and Treatment, M. Clin. North America **28**:968-977 (July) 1944.

(*a*) The two most common types of nevi are, first, the small deeply pigmented flat (junction) type, which may or may not contain hairs; and, secondly, the soft, smooth, slightly elevated, moderately pigmented mole containing hairs.

(*b*) The ordinary pigmented nevus is benign and need not be removed except for cosmetic purposes. It is probably good practice, however, to remove deeply pigmented nevi, whether flat or elevated, which occur on the sole of the foot or in other regions where they are likely to be subjected to trauma, even though trauma has yet to take place. On the other hand, the occasional nicking of an ordinary hairy pigmented nevus, as in shaving, in my own experience is harmless and does not call for any treatment. If secondary infection supervenes, however, then the nevus should be removed as soon as this infection has subsided.

16. Montgomery, H., and Stegmaier, O. C., Jr.: Histopathologic Studies of Pigmented Nevi in Children, J. Invest. Dermat. **20**:51-64 (Jan.) 1953.

17. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

(*a*) The treatment of small nevi by electrolysis or carbon dioxide snow is generally accepted. Small lesions can be removed by thorough electrolysis. The practice of partial removal, however, such as removal of the hair from the center of the lesion or superficial electrolysis, is not without danger. We have seen several cases in which an apparently benign nevus had been incompletely removed by electrolysis, which was followed shortly by the development of melano-epithelioma (malignant melanoma).

(*b*) Most investigators are agreed that when a nevus undergoes malignant change the earliest changes, in the majority of the cases, are seen in nevus cells at the epidermal cutis junction. Exceptionally, the first malignant changes are seen in nevus cells deep in the cutis, in the so-called intradermal type of nevus.

18. Pack, G. T., (and others): Multiple Primary Melanoma: A Report of 16 Cases, Cancer **5**:1110-1115 (Nov.) 1952.

(*a*) Survey of 1,000 adult humans by Pack and Lenson revealed that the average individual had 15 pigmented moles.

(*b*) Out of 1,250 [melanoma] patients 1.28% have shown evidence of multiple primary lesions.

19. Pack, G. T.: A Clinical Study of Pigmented Nevi and Melanomas, in The Biology of Melanomas, New York, New York Academy of Sciences, 1948.

For several years, I plotted the incidence and distribution of pigmented moles among students and, in summary, I may say that the average individual has approximately twenty visible pigmented moles by adulthood.

20. Pack, G. T., and Livingston, E. M., editors: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, Vol. 3, The Treatment of Pigmented Nevi and Melanomas, pp. 2071-2094.

(*a*) Melanomas are of frequent occurrence on the soles of the feet and on the genitalia, in which regions nevi are seldom observed. This finding may be of therapeutic significance.

(*b*) It is thought best to remove all darkly pigmented nevi in infancy and childhood.

(*c*) Although electrocautery or electrodesiccation is eminently satisfactory for removal of some pigmented lesions of the skin, notably the epithelial papillomas, there is an element of danger in removing the true mole by this technique unless the operation is radical. Perhaps thousands of such true nevi are treated by dermatologists without mishap for every one that recurs as malignant melanoma, but the sequence of malignant transformation of an apparently quiet nevus following incomplete electrodesiccation has occurred with unpleasant frequency in the case histories at our disposal.

(*d*) It is safe to cut through pigmented nevi in children in performing multiple stage operations (of large nevi) but this should never be done after the age of puberty.

21. Schamberg, J. L., in discussion of Montgomery, H.: Histopathologic Studies of Pigmented Nevi in Children, J. Invest. Dermat. **20**:51-64 (Jan.) 1953.

We cannot always differentiate clinically between the benign intradermal or intraepidermal nevus.

22. Slaughter, D. P.: Superficial Tumors of the Head and Neck Area, Surg. Clin. North America **28**:69-81 (Feb.) 1948.

(*a*) There is no way absolutely to diagnose a mole that has become malignant except by microscopic definition. Experts with wide experience have a good percentage of clinical accuracy, but it is not perfect.

(*b*) There is considerable mythology and misunderstanding about the treatment of moles. There is much popular fear that disturbing a mole in any way may be dangerous. In my personal experience, and in the literature, there is no authenticated instance of a benign neuro-nevus becoming malignant after incomplete removal with the electric needle, cautery or excision. Close scrutiny of such supposed occurrences will almost invariably show that the mole was malignant in the first place, and usually treatment was instituted because of the changes incident to unrecognized malignant transformation.

(*c*) Dermatologists have removed thousands and thousands of moles with acid, carbon dioxide snow, electrocautery and so forth, without untoward occurrences. Removal of moles on the face for cosmetic reasons by these methods would seem to be perfectly safe. There are two disadvantages to such procedures: (1) no tissue is removed for microscopic section, and (2) the destruction of the lesion is almost always incomplete. The safest procedure is total removal of the mole by careful excision.

(*d*) If the mole is being removed for prophylactic purposes or for diagnosis in the case of doubt, then excision is mandatory. An oval incision about the mole, a millimeter or so from its edge and cutting well under it, is perfectly adequate removal.

23. Spitz, S.: Melanomas in Childhood, Am. J. Path. **24**:591-609 (May) 1948.

Since metastases from juvenile melanomas occur only rarely, conservative surgery, rather than the radical surgery usually indicated for adult melanomas, seems justified.

24. Sulzberger, M. B., and Baer, R. L.: Some Common Errors in the Management of Skin Diseases, in The 1951 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1952.

(*a*) Pigmented nevi which annoy because of their unsightliness, may be removed surgically if the cosmetic result of excision can confidently be expected to constitute a distinct improvement. On the other hand, the common small, soft, fibromatous nevi of different sizes (especially when bearing hair and when situated on the face or trunk) can safely be treated with various selected forms of destruction such as repeated applications of the fitted carbon dioxide pencil, one or several superficial electrodesiccations

or repeated painting with escharotics such as trichloracetic acid. Sometimes the preceding removal of the heavier hairs in the nevus by the needle of electrolysis or electrocoagulation is not only desirable but essential.

(*b*) It is our conviction, based on the sums of our own observations and those of most of our dermatologic colleagues, that these forms of treatment are entirely safe in properly selected lesions, but are likely to be eminently unsafe when incorrectly applied, e. g., to lesions already showing signs of inflammation or of rapid growth. In contrast to the quiescent, soft, hairy brown nevus, such lesions are likely either to possess high potentialities for malignancy or already to have developed the beginning of malignant alterations. If and when they are to be treated, they must be removed by adequate excision, even if there is a possibility or likelihood of an undesirable cosmetic result.

25. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, Ed. 10, St. Louis, C. V. Mosby Company, 1939.

Growths [nevi] of dime size or smaller may readily be destroyed by means of the post electric cautery, or solid carbon dioxide.

In hairy growths the hairs may be removed by electrolysis, thus ameliorating the disfigurement, or the lesions may be excised in toto, and the area covered with skin grafts.

26. Swerdlow, M.: Nevi: A Problem of Misdiagnosis, Am. J. Clin. Path. **22**:1054-1060 (Nov.) 1952.

The clinical diagnosis of nevus of 551 lesions was correct in only 61 per cent of the lesions, and of 454 lesions diagnosed pathologically as nevi, the clinical diagnosis was correct in only 74 per cent.

These figures do not compare with those of Becker, who found that of 710 lesions diagnosed clinically as nevi, 80 per cent were correct, and of 649 lesions diagnosed pathologically as nevi, 87 per cent were correct. This difference may possibly be explained by the experience of the examiners. In Becker's series the diagnoses were made by dermatologists, dermatology graduate students and a few general practitioners. In this series, the diagnoses were submitted by practitioners in all specialties.

27. Traub, Eugene F.: The Pigmented, Hairy and Warty Nevi and Their Relationship to Malignancy, South. M. J. **40**:1000-1005 (Dec.) 1947.

While clinically and microscopically such junction nevi present from birth or early infancy appear absolutely similar to those junction nevi which appear later in life, nevertheless, they must possess vital differences that we thus far have not detected. Their difference in prognosis is so striking that this must be so. Therefore, it is obvious that we must have two dissimilar lesions that we classify as junction nevi.

28. Traub, E. F., and Keil, H.: The "Common Mole": Its Clinicopathologic Relations and the Question of Malignant Degeneration, Arch. Dermat. & Syph. **41**:214-252 (Feb.) 1940.

(*a*) The growths that we have designated as junction type nevi represent what we consider potentially malignant melanomas. It is our belief that incomplete treatment of these growths by electrolysis, desiccation, coagulation or surgical removal is a dangerous procedure which may be followed by dire results.

(*b*) There are occasional observers who believe that the (intradermal) nevus cells do not undergo malignant change but that this complication occurs only in cells at the epidermodermal junction. Our observations are in accord with this view.

(*c*) We have sought for lesions located on the lower extremities which might be catalogued as genuine intradermal moles, but our search thus far has been fruitless.

(*d*) A questionnaire was submitted to about one hundred and twenty members of the American Dermatological Association. The questions proposed were: 1. Have you ever seen a small common hairy mole become malignant? 2. Have you ever seen a histologically proved benign cellular nevus (mole or pigmented mole) become malignant subsequently? Of the ninety-three dermatologists [answering], eighty-five had not observed malignant change in a small common hairy mole, despite manifest opportuni-

ties to witness such transformation. In addition, this group has never seen a histologically proved benign cellular nevus become malignant subsequently. A few had seen clinically benign pigmented lesions undergo malignant change; some of these were doubtful that such lesions had been benign from the beginning in the pathological sense; most of these lesions were on the lower extremities.

29. Webster, J. P.; Stevenson, T. W., and Stout, A. P.: Surgical Treatment of Malignant Melanomas of Skin, Surg. Clin. North America **24**:319-339 (April) 1944.

In 104 cases [of melanomas] with complete information, 65 per cent started from pre-existing moles. Thirty-five per cent seemingly arose from normal skin. In the 68 cases preceded by a mole 36 had been traumatized (19 by physicians using chemical or physical methods).

Cauterization has been advocated as an ideal method of treatment. It has advantages in that the procedure takes but little time, is comparatively inexpensive, and requires little skill to perform, although much education is needed to have it understood by the profession that the cauterization must be sufficiently radical to destroy the entire lesion and must include a generous margin of normal tissue. We believe that radical surgical excision offers the best therapy for all of these lesions.

30. Wells, A. H.: Melanomata and Nevi, Minnesota Med. **33**:456-461 (May) 1950.

There is to my knowledge no histologic proof that melanomata have resulted from incomplete removal of a nevus.

PROFESSORS OF DERMATOLOGY IN AMERICAN MEDICAL SCHOOLS, 1867-1953

WALTER B. SHELLEY, M.D.
PHILADELPHIA

We should endeavor to create an influence which should secure instruction in our department by thoroughly competent men in all our schools of medicine, by men, where they can be obtained, whose whole study and practice are devoted to it. Fortunately but little remains to be done in this particular. The schools have been the first to recognize the claim of dermatology in this regard, and to furnish their students with the best opportunities of study at their command. Whereas hardly ten years ago, we had not a single officially recognized representative among the great body of medical instructors in the United States; we now have:

Professors, 4; *Clinical Professors*, 5; *Instructors*, 1; *Lecturers*, 6; *Total*, 16.

Professorships: Vermont, Bellevue, Chicago, Harvard.

Clinical Professorships: University of City of New York; College of Physicians and Surgeons; Long Island Hospital-College; University of Pennsylvania; Women's College of N. Y. Infirmary.

Lecturers: Missouri Medical College; Detroit Medical College; University of Louisville; Baltimore College of Physicans and Surgeons; Medical College of Ohio; Albany.

Instructors: Jefferson Medical College.

JAMES C. WHITE
American Dermatological Association
Presidential Address, 1877

THREE generations have passed since James C. White thus proudly sketched the early status of academic dermatology in the United States.[1] During that interval dermatology has shared in the vigorous expansion which has occurred in medicine and in medical education. Within the first generation following White's report at least 25 additional schools had acknowledged the special province of cutaneous medicine by establishing professorships of dermatology with appropriate sections or separate departments. In 1953, with but rare exception, each of the 72 approved medical schools in the United States had a division, section, or department of dermatology.

The remarkable genealogy of professors of dermatology in American medicine has never been published. In fact but few references * exist concerning the history of dermatology in specific medical schools. General medical histories and references accord the subject no attention. It was my aim to prepare a simple tabular chart listing the academic leaders in dermatology. The size of such a tabulation precludes other than a direct chronological presentation of names arranged according to schools.

Department of Dermatology, University of Pennsylvania Medical School.

* References 1 to 6.

Nearly all of the information has been obtained by inquiry of the deans of the medical schools. Without their help, and the co-operation of many of the departmental heads, little could have been learned. Most of the schools' reservoir of information was in the dusty catalogues and bulletins of bygone years. The paucity of information freely available makes it evident that more dermatologists should undertake to recount the story of the development of academic dermatology in their area. Too often rich funds of information are lost because individuals fear that only professional historians are prepared for such writing.

It has been necessary to make a number of arbitrary (and at times difficult) decisions regarding the incorporation of data in the table. These include the following:

1. Men holding joint or multiple titles such as "Professor of Electrotherapeutics and Dermatology" are not mentioned. Such conjoint title designation was a common early practice and indicated dermatology had as yet not assumed its distinctive position in the school concerned.

2. No separation is made between full professors and clinical professors. However, an attempt was made to list only the actual chief of the section or department.

3. The dates of tenure indicate the time, insofar as I could determine, that the men were in active charge of the department or teaching section. In many instances the men initially held a lower rank than that of professor. Moreover in several schools the present chiefs are not full professors. Acting heads of the department have been included only if these individuals later assumed full direction. Overlapping tenure dates are seen whenever it was not possible to discern from the data at hand the relative academic status of the individuals concerned.

4. Only the genealogy of professorships in present-day medical schools is given. Numerous private or small medical schools were extant years ago, but in the gradual evolution of medical education many dissolved or fused to form new schools. With the exception of New York University, I have not included the dermatologic story of these ancestral schools which are no longer in existence.

All beginnings become misty with the passage of time. Moreover, origins themselves may frequently be inexact, multiple, or diffuse. In reviewing the early days of academic dermatology one commonly encounters the misty, the diffuse, and the obscure. Yet a fairly accurate general picture may be obtained. Noah Worcester deserves our initial tribute as the first academic dermatologist in the United States. From 1843 to 1845 he served as Professor of General Pathology, Physical Diagnosis and Diseases of the Skin in the newly formed Cleveland Medical College (part of Western Reserve). Appropriately he wrote the first American textbook of dermatology, "A Synopsis of the Symptoms, Diagnosis and Treatment of the More Common and Important Diseases of the Skin," with 60 colored illustrations. A graduate of Dartmouth Medical School, Worcester had trained in St. Louis Hospital in Paris. He died in 1847 at the early age of 35, a victim of pulmonary tuberculosis.

A contemporary pioneer was Henry D. Bulkley, a New York physician specializing in skin disease. Bulkley has the distinction apparently of having given the first dermatologic lectures in America. These were given in the spring of 1841 at the College of Physicians and Surgeons in New York City. Another series of lectures was given by Bulkley in 1853 at the University Medical College (later to become New York University).

In 1867 this University Medical College in New York City established the first clinical professorship in America specifically limited to dermatology. Faneuil D. Weisse was given this appointment and thus heads the list in the accompanying Table. The College of Physicians and Surgeons (Columbia) shortly thereafter, in

Lineage of Professors of Dermatology in the Seventy-Two Approved Medical Schools in the United States *

1867-1880	
New York University	1867-1875—Faneuil D. Weisse
	1875-1888—Edward L. Keyes
	1888-1899—Henry G. Piffard
	1899-1913—John A. Fordyce
	1913-1925—William B. Trimble
	1925-1938—Howard Fox
	1938-1940—Edward R. Maloney
	1940-1949—Frank C. Combes
	1949 —Marion B. Sulzberger
Columbia University	1869-1879—William H. Draper
	1881-1907—George H. Fox
	1907-1912—George T. Jackson
	1912-1925—John A. Fordyce
	1926-1947—J. Gardner Hopkins
	1947-1950—A. Benson Cannon
	1950 —Carl T. Nelson
Harvard	1871-1902—James C. White
	1902-1911—John T. Bowen
	1911-1927—Charles J. White
	1929-1936—E. Lawrence Oliver
	1936-1947—C. Guy Lane
	1948 —Chester N. Frazier
University of Pennsylvania	1875-1911—Louis H. Duhring
	1911-1923—Milton B. Hartzell
	1927-1945—John H. Stokes
	1945 —Donald M. Pillsbury
University of Vermont	1876-1890—Robert W. Taylor
	1895-1896—William W. Seymour
	1896-1900—George T. Jackson
	1900-1903—Ellice M. Alger
	1903-1907—George G. Campbell
	1907-1912—Charles A. Peters
	1912-1930—Charles M. Williams
	1930-1948—Eugene P. Traub
	1948 —John F. Daly
University of Maryland	1879-1897—Isaac E. Atkinson
	1897-1927—Thomas C. Gilchrist
	1927-1935—Melvin S. Rosenthal
	1935 —Harry M. Robinson
1880-1890	
New York Medical College	1881-1892—P. E. Arcularius
	1893-1904—Henry M. Dearborn
	1908-1940—Frederick M. Dearborn
	1940-1948—H. Van Alstyne Cornell
	1948 —Eugene F. Traub
George Washington University	1883-1906—H. C. Yarrow
	1906-1924—Randolph Carmichael
	1924-1939—C. Augustus Simpson
	1939 —H. Ford Anderson
University of California	1884-1886—Benjamin Swan
	1886-1888—F. H. Terrill
	1894-1912—D. W. Montgomery
	1912-1940—Howard Morrow
	1940-1947—Hiram E. Miller
University of Illinois	1884-1891—Henry J. Reynolds
	1894-1915—William A. Pusey
	1919 —Francis E. Senear
University of Pittsburgh	1886-1906—J. C. Dunn
	1906-1909—John Burke
	1909-1917—W. B. Ewing
	1917-1919—Louis Swartz
	1919-1952—William H. Guy
	1952 —Frederick M. Jacob
State University of New York at New York City	1887-1903—Samuel Sherwell
	1903-1921—James M. Winfield
	1921-1939—Alfred Potter
	1939 —Arthur W. Grace

* Information regarding the University of Arkansas and the University of Louisville not available, except for names of the professors now incumbent: Ewell L. Thompson and Winston Rutledge, respectively.

*Lineage of Professors of Dermatology in the Seventy-Two Approved Medical Schools in the United States**—(Continued)

Western Reserve University	1888-1914	William T. Corlett
	1914-1952	Harold N. Cole
	1952 —	Herbert H. Johnson, Jr.
University of Buffalo	1888-1926	Grover W. Wende
	1926 —	Earl D. Osborne
Hahnemann Medical College	1889-1915	Edward M. Gramm
	1915-1948	Ralph Bernstein
	1948 —	H. Earl Twining
	1890-1900	
Jefferson Medical School	1890-1919	Henry W. Stelwagon
	1920-1947	Frank C. Knowles
	1947-1948	Edward P. Corson
	1948-1949	Clarence S. Livingood
	1950 —	Henry B. Decker
Northwestern University	1890-1917	Joseph Zeisler
	1917-1919	Frederick G. Harris
	1920-1940	Arthur W. Stillians
	1940-1950	Edward A. Oliver
	1951 —	Herbert Rattner
Woman's Medical College	1891-1907	Henry W. Stelwagon
	1907-1914	Milton B. Hartzell
	1914-1921	Frank C. Knowles
	1921-1923	Henry K. Gaskill
	1923-1936	Joseph V. Klauder
	1936-1941	Rose Hirschler
	1941 —	Carmen C. Thomas
University of Minnesota	1892-1912	Max V. Horek
	1912-1913	Burntside Foster
	1913-1929	Samuel E. Sweitzer
	1921 —	Henry E. Michelson
Boston University	1892-1917	John L. Coffin
	1917-1931	Wesley T. Lee
	1931-1943	Rudolph Jacoby
	1944-1952	John G. Downing
	1952 —	Herbert Mescon
University of Cincinnati	1894-1909	Augustus A. Ravogli
	1909-1918	Meyer L. Heidingsfeld
	1918-1941	Elmore B. Tauber
	1941-1947	Harry L. Classen
	1947 —	Leon Goldman
Cornell Medical School	1898-1916	George T. Elliott
	1916-1942	Hans J. Schwartz
	1942 —	George M. Lewis
Johns Hopkins University	1898-1927	Thomas C. Gilchrist
	1898-1929	J. Williams Lord
	1929 —	Lloyd W. Ketron
University of Texas	1898-1909	George H. Lee
	1910-1928	Earl D. Crutchfield
	1928-1942	William F. Spiller
	1942-1948	Chester N. Frazier
	1949-1953	Clarence S. Livingood
	1953 —	J. Frederick Mullins
University of Iowa	1899-1934	John B. Kessler
	1934-1936	James C. Kessler
	1936 —	Ruben Nomland
	1900-1910	
Baylor University	1900-1912	E. A. Blount
	1912-1929	Jesse B. Shelmire, Sr.
	1929-1943	Jesse B. Shelmire, Jr.
	1943-1949	Culver M. Griswold
	1949 —	Everett R. Seale
University of Colorado	1900-1917	Newton Wiest
	1911-1917	William H. Davis
	1911-1945	Arthur J. Markley
	1945 —	Osgoode S. Philpott
Yale University	1902-1920	Ralph A. McDonnell
	1920-1935	Alfred G. Nadler
	1936 —	Maurice J. Strauss
St. Louis University	1903-1910	John H. Duncan
	1910-1912	Martin F. Engman
	1913-1944	Joseph Grindon
	1950 —	Garold V. Stryker
Tufts College	1903-1913	James S. Howe
	1913-1916	Francis J. Keany
	1918-1929	Townsend W. Thorndike
	1930-1943	William P. Boardman
	1944-1952	John G. Downing
	1952 —	Bernard Appel

*Lineage of Professors of Dermatology in the Seventy-Two Approved Medical Schools in the United States**—(Continued)

Temple University	1904-1939	Edward B. Fineh
	1910-1919	Jay F. Schamberg
	1919-1931	Albert Strickler
	1932	Carroll S. Wright
University of Kansas	1904-1940	Richard L. Sutton, Sr.
	1940-1949	Charles C. Dennie
	1949	Richard L. Sutton, Jr.
University of Michigan	1905-1911	William E. Breakey
	1912-1947	Udo J. Wile
	1947	Arthur C. Curtis
Tulane University	1906-1920	Isadore Dyer
	1916-1926	Henry E. Menage
	1926-1941	Ralph Hopkins
	1941-1953	Martin T. Van Studdiford
Indiana University	1907-1924	Alembert W. Brayton
	1925-1941	Frank W. Cregor
	1943	Frank M. Gastineau
Wayne University	1907-1920	Andrew P. Biddle
	1920-1922	H. R. Varney
	1922-1937	Robert C. Jamieson
	1937	Loren W. Shaffer
Ohio State University	1908-1942	Charles J. Shepard
	1942-1947	Burton Barney
	1950	Eldred B. Heisel
1910-1920		
University of Tennessee	1910-1911	James Brew
	1911-1933	Marcus Haase
	1933	Emmett R. Hall
Georgetown University	1910-1933	Henry H. Hazen
	1933	Frank J. Eichenlaub
University of Oklahoma	1910-1942	Everett S. Lain
	1942	Charles P. Bondurant
Howard University	1911-1944	Henry H. Hazen
	1944	Charles W. Freeman
Washington University	1912-1942	Martin F. Engman, Sr.
	1942-1951	Richard S. Weiss
Stanford University	1912-1944	Harry E. Alderson
	1949	Eugene M. Farber
Medical College of Virginia	1913-1938	Edward McGavock
	1938-1947	Thomas W. Murrell
	1947	Richard W. Fowlkes
Marquette University	1913-1917	Albert H. Purdy
	1917-1921	Robert G. Washburn
	1921-1951	Simpson M. Markson
	1951	Harry R. Foerster
Medical College of South Carolina	1915-1934	J. Austin Ball
	1934	John van de Erve, Jr.
Emory University	1915-1916	Bernard Wolff
	1916-1922	Miller P. Hutchins
	1922-1944	Cosby Swanson
	1944-1947	Jack W. Jones
	1947	Herbert S. Alden
Loyola University (Chicago)	1916-1918	Kazimir A. Zurawski
	1918-1919	Edward A. Fischkin
	1919-1920	Arthur W. Stillians
	1920-1923	William A. Quinn
	1923-1944	B. Barker Beeson
	1944	Cleveland J. White
University of Nebraska	1919-1935	Alfred Schalek
	1935-1949	Charles C. Tomlinson
	1949	Olin J. Cameron
1920-1953		
College of Medical Evangelists	1921-1923	Ralph R. Campbell
	1924-1927	Edward D. Lovejoy
	1928-1948	Samuel Ayres, Jr.
	1948	Clement E. Counter
University of Virginia	1924-1950	Dudley C. Smith
	1951	Edward P. Cawley
Vanderbilt University	1925-1927	James M. King
	1927	Howard King
University of Rochester	1925-1944	Albert R. McFarland
	1944-1952	Henry C. Shaw
	1952	Elmer Tuttle
University of Wisconsin	1925-1946	Otto H. Foerster
	1946	Sture A. M. Johnson
University of Chicago	1927-1942	Samuel W. Becker
	1942	Stephen Rothman

Lineage of Professors of Dermatology in the Seventy-Two Approved Medical Schools in the United States *—(Continued)

University of Oregon	1928-1952	—Lyle B. Kingery
	1952	—Thomas B. Fitzpatrick
Louisiana State University	1931-1936	—Joseph N. Roussel
	1937-1953	—James K. Howles
	1953	—Charles B. Kennedy
University of Southern California	1932-1945	—Kendal P. Frost
	1945	—Maximillian R. Obermayer
Medical College of Georgia	1933-1947	—G. T. Bernard
	1947	—J. Malcolm Bazemore
State University of New York at Syracuse	1933	—Leon H. Griggs
Albany Medical College	1936	—Rudolph Ruedemann, Jr.
Duke University	1937	—J. Lamar Callaway
Chicago Medical School	1939-1949	—Maurice Oppenheim
	1950	—David M. Cohen
Bowman Gray School of Medicine	1941	—William L. Kirby
Southwestern Medical School	1943	—Bedford Shelmire
University of Utah	1943	—William J. Morginson
Meharry Medical College	1943	—Charles M. Hamilton
Medical College of Alabama	1945	—Ray O. Noojin
Creighton University	1948	—John A. Borghoff
University of Washington	1949	—Joseph W. Shaw

1869, appointed William H. Draper as Clinical Professor of Diseases of the Skin. The example had been set, and, as White has stated, within 10 years nine professors had been appointed. Some of the early appointees do not appear in the table since they represented schools no longer in existence. An example is James N. Hyde, who became professor at Rush Medical College in Chicago in 1873.

Special attention should be directed to James C. White, who in 1871 was the first in America to receive the title of full Professor of Dermatology. It was at Harvard Medical School that this chair of dermatology was first created. This single act, probably more than any other, gave university status to the fledgling subject of dermatology. For more than 30 years White served as professor at Harvard and was a guiding power in American dermatology.

In the ensuing years an ever-widening circle of schools recognized dermatology as a subject worthy of the medical students' special attention. In fact the numerical rise of professorships directly reflects the dual growth of specialism and medical education in America. Today, at the acme of specialistic teaching and research, every medical school has well-trained men designated for the transmission of dermatologic knowledge.

It is fitting to close with a silent tribute to these our academic leaders in American dermatology who in the last century have so rapidly advanced the position of our specialty. May their influence be a challenge to us in the future.

REFERENCES

1. White, J. C.: Dermatology in America, Arch. Dermat. **4**:1, 1878.

2. Goldman, L.: Development of Dermatology in Ohio, Ohio M. J. **46**:989, 1950.

3. Robinson, H. M.: A Short History of Dermatology as It Progressed in Baltimore, Bull. School Med. Univ. Maryland **37**:9, 1952.

4. Rattner, H.: The Department of Dermatology, Northwestern University Medical School, Quart. Bull. Northwestern Univ. M. School **27**:145, 1953.

5. Michelson, H. E., and Lynch, F.: Dermatology in the First Century of Medicine in Minnesota, Minnesota Med. **36**:375, 1953.

6. Friedman, R.: The History of Dermatology in Philadelphia, to be published.

RADIOBIOLOGIC MECHANISMS IN THE SKIN

MYRON H. KULWIN, M.D.
AND
HANS M. BULEY, M.D.
CHAMPAIGN, ILL.

INTEREST in the effects of ionizing radiations on cutaneous structures was aroused in dermatologic circles shortly after the original discovery of the roentgen ray itself, inasmuch as the untoward effects on the skin were forcibly called to the attention of dermatologists. Since that time, the use of x-rays in dermatologic therapy has developed along parallel lines with the ever-increasing fund of knowledge about the basic physical aspects of this type of radiation. Dermatologists have pioneered not only in the use of x-radiation but also in the clinical investigation of alpha-and gamma-ray-emitting substances.

The clinical effects, both gross and microscopic, of these various radiations have been well classified and catalogued over the years. Reasonably accurate dosage schedules have been established, and predictable effects can be produced at will.

Similarly, in practically all of the specialized fields of biology—bacteriology, parasitology, botany, etc.—experimental use has been made of the different types of ionizing radiations to probe the metabolic activities of living systems. These explorations have resulted in the accumulation of much knowledge about the effects of ionizing radiations on living structures—the radiobiologic effects.

Concomitant with this growth and maturation process, similar experimental exploration has been carried out by physicists, radiation chemists, and others on purely physical and chemical problems dealing with the basic nature of ionizing radiations, their parameters and their effect on nonliving substances and systems. Slowly the borders of these research areas have spread in a peripheral fashion to overlap on a common meeting ground—the study of the fundamental processes involved in radiobiologic mechanisms.

During the past 15 years, the use of ionizing radiations in dermatological therapy has become increasingly limited, often because of conclusions arrived at from incomplete premises. For example, the use of x-ray therapy in the treatment of superficial mycoses has been almost completely abandoned, because it is well known that fungi, in vitro, are not killed by therapeutic doses of x-rays. However, no attention was paid to the possibility that the x-rays might alter the medium to such an extent as to render it unsuitable for propagation of mycelial growth. It is because of potentialities such as this that dermatological x-ray therapy must be reconsidered and reevaluated in the light of the latest radiobiologic findings.

From the Department of Dermatology, The Christie Clinic.

CHEMICAL CONSIDERATIONS

The changes which occur when tissue is irradiated can best be understood if the tissue—skin, for example—is considered to be a dilute aqueous solution of many organic and inorganic substances. The following description is a summary of the prevailing hypotheses dealing with observed radiochemical-induced changes.

The path of an ionizing particle may be called the ionization track, and the nature of the particle will determine the density of ionization along the track. In the case of radiation of low penetrability (such as an alpha emission) the ionization density will be comparatively great, whereas with a more penetrating beta radiation the density of ionization will be less.* It has been calculated † that in the case of a beam of alpha radiation, the centers of ionization processes along the track are 9 A. units apart, with beta radiation of radium 150 A. units apart, and with gamma radiation, 5,000 A. units. It is evident, then, that because of the greater density of ionization reactions (or formation of ion pairs) with alpha rays at equal incident doses, the possibility of producing a skin-necrotizing reaction is much greater than in the case of gamma radiation, in which a comparable quantity of ion pairs are spread through a greater volume of tissue, thus reducing the probability of so intense a reaction. This is a restatement in physical terms of information which can be seen in a comparative study of depth-dosage curves for various qualities of radiation. It is a well-known clinical fact that by increasing the hardness of a narrow beam of radiation (and thus spreading the number of ionizations which take place through a greater depth of tissue), the dosage can also be increased without producing additional destructive effects.‡

If a beam of ionizing radiation is passed through pure water, certain physicochemical changes are induced in the molecular structure of the water. Part of the beam's energy is transferred to the water, ejecting an electron and producing reaction (1).

$$H_2O + R\dot{o} \rightarrow H_2O^+ + e \qquad (1)$$

Inasmuch as the H_2O^+ is very unstable, it readily hydrolyzes (2).

$$H_2O^+ \rightarrow H^+ + OH^0 \qquad (2)$$

Thus, the track of ionization will be sheathed with a layer of hydrogen ions and hydroxyl radicals. It has been estimated † that this layer is 8 A. units from the path of ionization itself.

Subsequently, the free electron released in reaction (1) combines with another molecule of water, producing hydrogen radicals and hydroxyl ions (3).

$$H_2O + e \rightarrow H^0 + OH^- \qquad (3)$$

This reaction occurs at a distance of about 150 A. units from the ionization track.

* This is really more complex; density of ionization depends on the speed and charge of the particle, as does penetration. Thus the relationship between ionization density and penetration is not fixed; e. g., a 300 mev deutron has good penetrability and also produces a densely ionized track.

† Magee, J. L.: A Critical Survey of the Theory of Radiation Chemistry of Aqueous Solutions, read at the Radiation Research Society Meeting, Iowa City, June 22-24, 1953.

‡ There are probably two effects involved here; even for equal tissue doses, the tolerance for high energy rays is greater.

If free oxygen is dissolved in the water—as is usually the case in living systems—further reactions occur, resulting in the formation of hydrogen peroxide, with intermediate formation of a hydroperoxyl radical (4) and (5).[2]

$$H + O_2 \rightarrow HO_2 \quad (4)$$

$$H + HO_2 \rightarrow H_2O_2 \quad (5)$$

In the case of x-rays, for example, the quantity of hydrogen peroxide formed depends upon the concentration of dissolved oxygen.[3] Latarjet[4] has found that after 600,000 r are delivered to a volume of water, about 6 γ of hydrogen peroxide per cubic centimeter may be demonstrated in the presence of dissolved oxygen, while in its absence only 0.24 γ per cubic centimeter is found. Moreover, it is probable that this latter small quantity results from the presence of non-removable organic contaminants.

Hydrogen peroxide has been considered to be of basic importance in the production of radiobiologic effects because of repeated observations that anoxic living systems are generally more resistant to the effects of ionizing radiations than comparable oxygenated systems. Five times the dose is necessary to produce an equivalent killing effect when irradiation of bacteria is done in the absence of oxygen than when oxygen is present.[25] Cells under anaerobiosis are relatively insensitive to radiation.[26] Torula cremonas is more sensitive to x-rays in the presence of oxygen.[27] Cells forming the margins of carcinomatous cell masses are more sensitive to gamma radiation than the central cells.[28] A reasonable explanation for this fact is that the marginal cells have a more abundant oxygen supply and are, therefore, more radiosensitive.

Undue emphasis, however, must not be placed on hydrogen peroxide being the only mechanism of radiobiologic effects. There is no doubt that hydrogen peroxide in certain cases can account for some of the effects,[29] but there are sufficient examples of substances not sensitive to hydrogen peroxide which show marked radiosensitivity.[30] Moreover, catalase, one of the most powerful and radio-resistant enzymes ubiquitously present in tissue,‖ and peroxidase are both capable of decomposing hydrogen peroxide and other peroxides which may be formed.

Equally chemically active in ionized water are the hydrogen and hydroxyl radicals, having very unstable electronic structures by virtue of their excess and deficiency of peripheral electrons. Because of their electrical imbalance, they will strongly tend to reestablish their electric equilibrium and will have a great affinity for each other. The excess electron of H^0 will tend to replace that lacking in OH^0. Keeping in mind the fact that the radicals H^0 and OH^0 are formed in two successive steps[7] and approximately at a distance of slightly over 100 A. units from each other, the probability of a recombination before meeting an alien acceptor molecule will be small indeed. For example, hydrogen peroxide may be formed as previously mentioned (4) and (5).

Other in vitro reactions which may occur[8] are oxidations such as ferrous to ferric ion,

$$Fe^{++} + OH^0 \rightarrow Fe^{+++} + OH^-, \quad (6)$$

and iodide to iodine,

$$I^- + OH^0 \rightarrow I + OH^-, \quad (7)$$

and reductions such as ceric to cerrous ion,

$$Ce^{++++} + H^0 \rightarrow Ce^{+++} + H^+. \quad (8)$$

‖ References 5 and 6.

An example of this type of oxidation-reduction reaction affecting a living system is the production of lenticular cataracts by ionizing radiations. Bellows [10] and von Euler and Martin ¶ have shown that the sulfhydryl content of lens protein is diminished in cataract. Barron [9] interprets this finding to mean that radiation may oxidize sulfhydryl groups in lens protein, producing intermolecular disulfide (—S—S—) bridge formation with consequent polymerization, thickening of the protein molecules, and eventual production of opacity.

BIOLOGICAL CONSIDERATIONS

Radioprotection.—Many clues to possible radiobiologic mechanisms can be found in studies of radioprotection. Theoretically, we may postulate that chemical protectants may act by one of four methods: (1) the agent may compete for free oxidizing radicals which are produced by ionization of water; (2) there may be a decreased formation of these radicals due to the presence of these agents; (3) there may be a shift in the redox potential of certain critical cellular constituents, and (4) alterations in the metabolism of the animal may increase radiation resistance.

Barron,[15] for example, has suggested that all radiobiologic effects are due to the oxidation of sulfhydryl groups. As soluble compounds, such as cysteine and glutathione, they have an active role in such vital processes as mitosis, cell division, and cell growth. As fixed thiol groups, attached to proteins and nucleoproteins, they are components of enzymes, muscle fiber, and skin. When radiation is used in small doses, the effects may be limited to those produced by oxidation of these sulfhydryl groups—namely, inactivation of enzyme systems and inhibition of cell division and growth. Further irradiation will cause denaturation and precipitation of the protein structure. The former changes are reversible with addition of further sulfhydryl-containing compounds, such as cysteine and glutathione. The latter damage is irreversible and recovery will depend upon the rate of protein synthesis.

It is possible that certain radioprotectants may exert their effect by producing hypoxia. Cysteine, for example, a sulfhydryl-containing radioprotectant of proved value,# has been shown to produce hypoxia in dogs, perhaps mediated through formation of cysteic acid.* However, increasing the atmospheric oxygen will inhibit the protecting effect of cysteine. If, on the other hand, the atmospheric oxygen content is increased prior to, but not during, irradiation, cysteine protection is not impaired. Thus, the protecting effect of cysteine may also be partly or wholly ascribed to oxygen starvation produced by the easily oxidized cysteine.

It has been demonstrated † that NaCN, sodium cyanide, considerably increases the survival rate of animals subject to lethal doses of radiation. The agent is most effective when injected immediately prior to irradiation. Malononitrile (which liberates CN^- ions) and NaN_3, sodium nitride, are also good protectors. Also, many amines [23] will protect cholinoxidase in vitro against the radiomimetic effect of nitrogen mustard. A decarboxylated derivative of cysteine, beta-mercaptoethyl-

¶ von Euler, H., and Martins, C. J., cited by Barron.[9]

References 6, 17, and 31.

* Salerno, P. R., and Friedell, H. L.: Studies on the Nature of the Protective Actions of Beta-Mercaptoethylamine and Cysteine Against X-Rays and a Nitrogen Mustard, read at the Radiation Research Society Meeting, Iowa City, June 22-24, 1953.

† References 19, 20, 21, and 22.

amine, for example, affords excellent protection[‡] against lethal doses of radiation in experimental animals. The protecting effect of cyanide may be due to a reduced oxygen consumption. To protect against radiation damage, the radiation has to take place shortly after the administration of cyanide, that is, when oxygen consumption is markedly reduced. The protecting effect is only minute when the cyanide is injected 15 minutes after irradiation.‡

General Cellular Effects.—In considering the radiobiologic mechanisms involved in producing effects in any tissue, it is necessary to break the target substance down into its basic component structural units, the cell types, and to discuss them individually. In speaking of the skin, we can limit our discussion to those structures about which relatively definite information is available.

The effect of ionizing radiations on the epidermal cells, similar to that in other radiosensitive tissue, is mediated by several possible mechanisms. Nuclear substance, as an illustration, is approximately 10-fold as radiosensitive as cytoplasm. The formation of nucleic acids, particularly deoxyribonucleic acid, is adversely affected by exposure to x-rays.[32] This has been demonstrated in the attempted incorporation of C^{14}-labelled formate into the nucleic acid purines and pyramidines in chick embryos following irradiation with a sublethal dose of x-rays. An inhibition of approximately 50% was found for the incorporation of the formate into deoxyribonucleic acid.§ That this effect as seen in vivo is not necessarily due to direct action of ionizing radiation on the affected structures but rather may also be mediated by a humoral mechanism must be considered.[33] When Ahlstrom‖ inoculated two sarcomata into a rat and shielded one, while directly irradiating the other with x-rays, the turnover rate of nucleic acid in the protected sarcoma was found to be diminished as well as that in the unprotected sarcoma, although to a lesser extent. Also, transfused blood from a strongly irradiated animal decreased the turnover rate of deoxyribonucleic acid in a recipient nonirradiated animal, whereas a blood transfusion from a nonirradiated donor had a lesser effect. On the other hand, it has been demonstrated that there is no visible clinical evidence of an indirect effect of ionizing radiation seen on the contralateral side when roentgen therapy is administered to a unilateral field for treatment of inflammatory diseases of the eyelids.[34] This finding has been borne out in a general pattern for all acute inflammatory diseases of the skin.

Similarly, there is a marked production of chromosomal aberrations following x-irradiation. It is interesting to note that mice exposed to an external source of pure beta radiation, such as a radioactive phosphorus plaque, and killed immediately after exposure already show clumping of nuclear chromatin in the basal layer of the epidermis, despite the fact that all other histologic detail is apparently normal.[11] The effect of ionizing radiation on chromosomal substance is closely correlated with the oxygen tension within the irradiated structure. This effect also holds true with a lowering of the temperature. Similarly, the formation of hydrogen peroxide, in an irradiated aqueous solution, will vary proportionately with the oxygen concentration and will also decrease as the temperature of the

‡ References 19 and 20.

§ Lavik, P. S., and Buckaloo, G. W.: Nucleic Acid Synthesis in X-Irradiated Chick Embryos, read at the Radiation Research Society Meeting, Iowa City, June 22-24, 1953.

‖ Cited by Hevesy.[33]

irradiated medium is lowered. These findings have led to the belief that chromosomal damage in irradiated tissue is due, at least in part, to hydrogen peroxide poisoning.

The effect of increased oxygen tension in potentiating radiobiologic effects is remarkable in the light of certain clinical considerations. It was recognized long ago, on a purely empirical basis, that treating a neoplasm with diathermy prior to administering roentgen therapy had an additive effect, and we may now assume this to be due, perhaps, to the increased oxygen supply provided by the heat-induced hyperemia. Likewise, it is a well-recognized clinical observation that acute inflammatory processes respond more readily to smaller doses of x-radiation than do chronic inflammatory lesions, and, as the acuity of the process subsides, larger doses are necessary to produce desirable effects. This again may now be explained on the basis of the greater blood supply of an acutely inflamed lesion as compared to one of long duration.

The importance of the permeability of cellular membranes in metabolic activities within the cell is well known. The effect of x-radiation on cell membrane permeability has been the subject of investigation in recent years by several authors. Ting and Zirkle [34] found that after treatment with 33,000 r, human erythrocytes became permeable to the univalent ions of sodium and potassium but remained substantially impermeable to the divalent ion of magnesium. Hevesy and Zerahn [35] showed that irradiation with a dose of 30,000 r influenced the amount of P^{32} and K^{42} (radioactive phosphorus and potassium) migrating daily from yeast cells into a nutrient solution to a minor extent only. Lindemann [36] examined irradiated erythrocytes under the electron microscope and observed a denaturation of the erythrocyte membrane. He felt that this phenomenon may be the result of a colloid chemical alteration under the influence of x-rays. Lindemann's observations, however, have been questioned by Graul,[38] who suggests that some of the findings may be artefacts produced either by the beam of the electron microscope or in the processing of the erythrocytes.

Pigment-Forming Structures.—Increased formation of melanin in postirradiated skin is a recognized clinical fact, and the mechanism of this phenomenon can now be theoretically explained on the basis of knowledge of radiobiologic changes. In the human skin, tyrosine is the precursor of melanin, and the conversion of the former to the latter occurs in the presence of the enzyme tyrosinase and is catalyzed by copper.[13] The copper in the skin, however, is bound to sulfhydryl-group-containing proteins and is thus rendered powerless to catalyze the tyrosine-melanin reaction. Under the influence of ionizing radiations, the copper-protein complex may be disturbed by oxidation of the sulfhydryl groups to disulfide linkage, thus freeing the copper to take part in the formation of melanin. This theory has been borne out to the point of demonstrating a marked, rapid decrease in the number of sulfhydryl groups in postirradiated skin as compared with nonirradiated controls.[37] This mechanism must be distinguished from other reactions, such as the "darkening phenomenon" and increased rate of oxidation with increased temperature, which may partially account for pigment production following exposure to nonionizing ultraviolet radiation.

Hair Follicles.—In certain experimental animals,[14] x-irradiation will depigment hair and eventually cause epilation if the dose is sufficiently high. This phenomenon

of x-ray-induced graying has been investigated thoroughly by Chase,[14] and more recently has been utilized [16] in certain radiobiologic studies. It has been observed that the dose of x-rays necessary to depigment hair will vary directly with the coarseness of the subject's hair, being lowest in fine-furred animals such as the mouse and higher in coarser-haired subjects such as the guinea pig. Because of the coarseness of human hair, the depigmenting dose usually far exceeds the epilation dose.

In those rare instances in which hair regrowth occurs after administration of a skin-damaging dose, the regrowth will usually be gray. We have recently had the opportunity to see a case in which 3,000 r were administered in divided doses to part of an eyebrow area in an intensely black-haired patient in treatment of a basal cell epithelioma. After the radiodermatitis had subsided, there occurred a patchy regrowth of pale gray hair which was sharply defined against the black background of the remainder of the eyebrow. Zeligman [16] has made similar observations in children epilated for treatment of tinea capitis.

The specific mechanism of radiation-induced depigmentation is unknown, although we may postulate that it is mediated through oxidation of some sulfhydryl-containing enzyme. This concept was suggested by experiments with cysteine hydrochloride. When this substance was administered subcutaneously to mice prior to irradiation, the graying effect was notably inhibited.[17] It has been recently demonstrated that local anoxia in mouse skin will increase the dosage of x-ray required to produce epilation two to threefold.

There also appears to be a marked variation in radiosensitivity of the hair follicles correlated with the hair growth cycle. Hair growth in the black mouse, for example, occurs in well-defined growth periods (anagen-catagen phases) followed by a resting period (telogen phase). It has been established [14] that epilation occurs more readily in the stage of rapid growth than during that of latency, whereas graying is more readily induced during latency than during active growth phases.

Glands.—The radiobiologic mechanisms through which glandular secretions are altered is one of the many as yet unprobed problems of dermatological interest. Only recently, histochemical techniques have been developed to assay various intracellular constituents, and it may be that the effect of ionizing radiations on the multitudinous intracellular metabolic systems may be reflected indirectly in the quality and quantity of cellular secretions and excretions.

COMMENT

When all due consideration is given to the radiobiologic research which has been done, it becomes obvious that radiation effects are not simply due to a projectile striking a target. This has been most interestingly pointed out by Zirkle [12] in the following manner: If a dose of 10,000 r is delivered to tissue, this will correspond to about 840,000 ergs (or 0.02 cal. or 5.2×10^{17} electron volts) per gram of soft cellular substance. This dose will, of course, produce many drastic changes in the tissue, despite the fact that such a small amount of energy per unit mass delivered in the form of heat would have no deleterious effects. An energy of approximately 32.5 electron volts is required to produce an ion pair in air, and if it is assumed that an equal amount of energy is required in the cell, then the dose of 10,000 r will produce 1.6×10^{16} ion pairs per gram. Since the average

cell contains about 3×10^{22} molecules per gram, it is evident that only about one-millionth of the molecules are activated! Thus the presence of some intermediary changes precipitated by an initial trigger-type reaction is necessarily postulated.

Quite often, the magnitude of x-ray dosage employed in radiobiologic investigation is so large as to be confusing to one accustomed to using more moderate dose levels for therapeutic purposes. It must be remembered, however, that many of the living systems, such as yeasts and some fungi, utilized in radiobiologic experiments are apparently refractory to smaller doses. This must not be construed, however, to mean that smaller doses are biologically ineffective. It has been demonstrated, for example, by Forssberg,[39] that a dose of 1×10^{-4} r may affect cellular growth. The differences in dosage employed in various radiobiological investigations must therefore be accepted prima facie in the present state of research.

Generally, however, it is apparent on the basis of present knowledge that certain basic mechanisms operate in producing all radiobiologic effects, the nature of which will depend on the physical, chemical, and biological characteristics of the target structure.

REFERENCES

1. Dainton, F. S.: On the Existence of Free Atoms and Radicals in Water and Aqueous Solutions Subjected to Ionizing Radiation, J. Phys. & Colloid Chem. **52**:490-517, 1948.

2. Burton, M.: Elementary Chemical Processes in Radiobiological Reactions, in Symposium on Radiobiology, edited by J. J. Nickson, New York, John Wiley & Sons, Inc., 1952, p. 120.

3. Hervé, A., and Bacq, Z. M.: Changes in the Effects of X-Irradiation by Certain Chemical Compounds: Theory, Experiments, J. Belge radiol. **3**:524-545, 1952.

4. Latarjet, R.: Mécanismes de l'action des rayons ionisants sur l'eau, Compt. rend. Acad. sc. **214**:73-75, 1942.

5. Forssberg, A.: Action of Roentgen Rays on Enzyme Catalase, Acta radiol. **27**:281-293, 1946.

6. Forssberg, A.: Mechanism of the Action of X-Rays on Enzymes in Water Solution, Nature, London **159**:308-309, 1947.

7. Lea, D. E.: Action of Radiation on Living Cells, Cambridge, Cambridge University Press, 1946.

8. Zirkle, R. E.: Relationships between Chemical and Biological Effects of Ionizing Radiations, Radiology **52**:846-855, 1949.

9. Barron, E. S. G.: The Effect of Ionizing Radiations on Some Systems of Biological Importance, in Symposium on Radiobiology, edited by J. J. Nickson, New York, John Wiley & Sons, Inc., 1952, p. 218.

10. Bellows, J. G.: Biochemistry of Lens; Influence of Vitamin C and Sulfhydryls on Production of Galactose Cataract, Arch. Ophth. **16**:762-769, 1936.

11. Snider, Ray S.: Histopathological Studies on Mice Following External Beta Ray Treatment, Manhattan District Declassified Document No. 583, November, 1946.

12. Zirkle, R. E.: Speculations on Cellular Actions of Radiation, in Symposium on Radiology, edited by J. J. Nickson, New York, John Wiley & Sons, Inc., 1952, p. 334.

13. Lerner, A. B., and Fitzpatrick, T. B.: Biochemistry of Melanin Formation, Physiol. Rev. **30**:91-126, 1950.

14. Chase, H. B.: Greying of Hair: I. Effects Produced by Single Doses of X-Rays on Mice, J. Morphol. **84**:57-80, 1949.

15. Bu'ey, H. M., and Kulwin, M. H.: Biological Assay of Exit Dose in Dermatological Roentgen Therapy, J. Invest. Dermat. **18**:397-402, 1952.

16. Zeligman, I.: Graying of Hair Following Epilating Doses of X-Rays, A. M. A. Arch. Dermat. & Syph. **66**:627-628, 1952.

17. Kulwin, M. H.: Effect of Cysteine Hydrochloride on Radiation-Induced Depigmentation of Mouse Hair, J. Invest. Dermat. **20**:237-243, 1953.

18. Barron, E. S. G.: Effect of Ionizing Radiations on the Activity of Enzymes, Brookhaven National Laboratory Document BNL-C-4, 1950, pp. 10-16.

19. Hervé, A., and Bacq, Z. M.: Cyanure et dose léthale de rayons x, Compt. rend. Soc. biol. **143**:881-883, 1949.

20. Hervé, A., and Bacq, Z. M.: Sulfocyanure, tocopherol et rayons x, Compt. rend. Soc. biol. **143**:1158-1159, 1949.

21. Hervé, A., and Bacq, Z. M.: Action protectrice du nitrure de sodium sur la léthalité des souris irradiées par rayons x, Compt. rend. Soc. biol. **144**:1124-1125, 1950.

22. Hervé, A.; Bacq, Z. M., and Betz, H.: Protection contre le rayonnement x par le cyanure et le nitrure de sodium, J. Chim. phys. **48**:256-257, 1951.

23. Colter, J. S., and Quastel, J. H.: Protection of Enzymes by Anticholine-Oxydases Against Inactivation by Nitrogen Mustard, Nature, London **166**:773-775, 1950.

24. Albers, E. C., and Buley, H. M.: X-Ray Therapy of Inflammatory Lesions of Eyelids, Illinois M. J. **95**:355-359, 1949.

25. Hollaender, A.; Stapleton, G. E., and Martin, F. L.: Effect of Oxygen on Response of Living Cells to X-Rays with Special Emphasis on Bacteria, Federation Proc. **9**:61-62, 1950.

26. Giles, N. H., and Beatty, A. V.: Effect of X-Irradiation in Oxygen under Pressure on Chromosone Aberration Frequency in Tradescantia Microspores, Genetics **35**:666, 1950.

27. Anderson, R. S., and Turkowitz, H.: Experimental Modification of Sensitivity of Yeast to Roentgen Rays, Am. J. Roentgenol. **46**:537-542, 1941.

28. Hevesy, G.: Ionizing Radiation and Cellular Metabolism, in Symposium on Radiobiology, edited by J. J. Nickson, New York, John Wiley & Sons, Inc., 1952, pp. 189-215.

29. Alper, T.: Hydrogen Peroxide and Indirect Effect of Ionizing Radiations, Nature, London **162**:615-616, 1948.

30. Dale, W. M.: Some Aspects of the Biochemical Effects of Ionizing Radiations, in Symposium on Radiobiology, edited by J. J. Nickson, New York, John Wiley & Sons, Inc., 1952, pp. 177-188.

31. Patt, H. M.; Tyree, E. B.; Straube, R. L., and Smith, D. E.: Cysteine Protection Against Irradiation, Science **110**:213-214, 1949.

32. Hevesy, G.: Effect of X-Rays in Incorporation of C^{14} into Desoxyribonucleic Acid, Nature, London **163**:869-870, 1949.

33. Hevesy, G.: Radioactive Indicators: Their Application in Biochemistry, New York, Interscience Publishers, Inc., 1948.

34. Ting, T. P., and Zirkle, R. E.: Kinetics of the Diffusion of Salts into and out of X-Irradiated Erythrocytes, J. Cell. & Comp. Physiol. **16**:197-206, 1940.

35. Hevesy, G., and Zeralin, K.: Effect of Roentgen Rays and Ultraviolet Radiation on the Permeability of Yeast, Acta radiol. **27**:316-327, 1946.

36. Lindemann, B.: Die Röntgen-Hamolyse als Structurproblem, Fortschr. Geb. Rontgenstrahlen **72**:366, 1950.

37. Frederic, J.: Étude histologique et histochimique de la peau de cobaye traitée par les rayons x, Arch. biol. **60**:79-101, 1949.

38. Graul, E. G.: Über den gegenwartigen Stand der strahlenbiologischen Forschung und deren allgemeine, biologische und medizinische Bedeutung, Hautarzt. **2**:193-201, 1951.

39. Forssberg, A.: Einige neuere Ergebnisse der Radiobiologie, Strahlentherapie **81**:162, 1950.

40. Strauss, J.; Kligman, A. M., and Greenberg, S.: Influence of Anoxia on the Depilation of Mouse Hair with X-Rays, J. Invest. Dermat. **22**:129-134, 1954.

RHUS TOXICODENDRON

Possibility of Systemic Toxic Effects

J. B. HOWELL, M.D.
ANDRES GOTH, M.D.
AND
GLADYS J. FASHENA, M.D.
DALLAS, TEXAS

IN RECENT years the question has been asked: Is it possible that systemic injury such as glomerulonephritis, the nephrotic syndrome,[1] periarteritis nodosa,[2] toxic encephalitis,[3] and even death * could be sequels of poison ivy dermatitis or of the administration of an extract of this plant. It is, therefore, expedient that we review the evidence for and against these possibilities or suspicions.

It is an accepted fact that drugs may cause the nephrotic syndrome. The newer antiepileptic medications, trimethadione [6] and paramethadione [7] must be added to the list of drugs causing the nephrotic syndrome.

In the American literature since 1770, there are only a few reports of systemic poisoning by the Rhus species of plants. For instance, Mr. Wilkes,[8] a student of medicine from Tennessee who was curious to test the truth of the statements made by some writers on the materia medica—that Rhus toxicodendron produces its poisonous effects only when applied to the skin—tried the experiment of drinking a strong decoction of the plant. He boiled the vine, with its leaves, and drank about a gill (118 cc.) of the fluid, taking care while preparing it not to let the vine come in contact with his person. It was taken after supper, and the next morning he found his face much swollen. The swelling continued to increase until his eyes were completely closed. In about 36 hours, the swelling and inflammation had disappeared. He slept nearly the whole time his eyes were closed, showing the narcotic action of the decoction.

Another early report is that of Dr. J. W. Moorman [9] of Hardingsburg, Ky. In 1866, he reported two cases, communicated to him by a professional friend. Two children ate about 1 pt. (550 cc.) of the fruit of Rhus toxicodendron in a few hours. They became delirious and stuporous, and in a short time vomiting commenced. The vomiting at first consisted of the partially digested fruit, and this was followed by a thick, tenacious fluid, the color of red wine. Generalized convulsions then appeared, accompanied by delirium. The respiratory rate was hurried, the pulse weak and rapid, and the pupils dilated. Emesis was induced, and a solution of sodium carbonate was freely administered. Both children recovered.

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* References 1, 4 and 5.

In 1867, Stokes [10] reported a case of a boy who drank tea made from the roots of Rhus toxicodendron. He became delirious and developed nervous twitchings, watery eyes, and an intense burning sensation in his stomach accompanied by an intolerable itching sensation associated with a measles-like rash and a high fever. He recovered.

Delirium, convulsions, and drowsiness are conspicuous by their absence in recent reports dealing with reactions following the phylactic or prophylactic use of extracts of Rhus toxicodendron. It is possible that the berries and the decoction prepared by boiling the vines and leaves contain a substance which is capable of causing these disagreeable reactions, and a fat solvent such as ether fails to remove that substance. Actually there is no proof that prolonged sleep, convulsions, and nervous twitchings were due to this cause.

Years ago a death [7] was reported from Chester, near Middleton, N. Y., from a rather unusual cause—the effects of ivy poisoning. The patient was a woman, 69 years of age, who came in contact with the plant in early July. Her whole system seemed to be profoundly affected by the poisoning, and death resulted after two months of great suffering.

John Culbertson [11] moved to Napa, Calif., from Dallas County, Iowa, in 1878, and was poisoned. He was advised to chew the leaves of the plant. He did so and died two days afterward from the poison.

John Culbertson had in all probablity a coronary occlusion or a cerebral hemorrhage rather than death in two days from chewing ivy leaves. Contact dermatitis from ivy is self-limited and heals in approximately two weeks, excepting a rare severe widespread eruption, which may persist four to five weeks, or when re-exposure cannot be prevented. Since the dermatitis lasted two months—in the case reported from Chester—infection, overtreatment dermatitis, or a sensitization dermatitis apparently complicated the eruption. Death, therefore, was due undoubtedly to other factors. A secondary infection could have resulted in nephritis and death. Postmortem examinations were not done in these two controversial cases, so the real cause of death will always be in doubt.

According to McNair,[12] an examination of 49 severe bed cases of Rhus dermatitis showed that 32, or 65.3%, were negative with respect to albumin and 17, or 34.6%, were positive, but the report on the positive cases revealed only a trace or a faint trace of albumin. One patient having albuminuria recovered from acute nephritis simultaneously with dermatitis.

Lowenburg,[8] in 1947, recorded the case of poisoning from a so-called overdose of the tincture of Rhus toxicodendron in a boy, aged 11. He developed a temperature of 109.2 F., gastritis, and damage to the central nervous system. Recovery was eventually complete.

This young man had been taking Rhus toxicodendron for seven weeks. After his recovery, he volunteered the information that he would forget from time to time to take the drops for a few days. When the drops were resumed, he would add drops for the days missed to the succeeding dose. The last dose—taken the day before his illness—was about 57 drops (3.5 cc.). The maximum dose, according to Lowenburg, recorded on the manufacturer's label for adults was 5 drops three times a day in a half glass of water. The patient used only a small amount of water in order to get it over with quickly. There had been an interval of 10 days without

taking the drops. The dose was stepped up by the patient from 45 to 55, 56, and 57 drops on successive days just prior to his admission. Lowenburg believed that he had hemorrhagic encephalitis, and the encephalitic condition was associated with intoxication from Rhus toxicodendron. All other possible etiologic factors were eliminated, Lowenburg states, and knowing the boy's extreme sensitivity, he could not help being convinced that the drug was the sole cause of the remarkable episode.

A neurologist with special interest in convulsive disorders was asked to study this case report and give his opinion of the possible relationship of the tincture to the illness. His remarks, in summary were:

It is significant that at about the age of 7 years this patient had medical attention because of enuresis and a bilateral congenital ureteral stricture which accounted for a few systemic ill effects. He was of small stature and had a speech defect. These items suggest that there was also a significant developmental or other defect in the nervous system.

On April 25, 1946, the boy had a bacilluria; then on May 4, he was admitted to the hospital with a fever of 105 F. At this time there was evidence of disease involving the left chest. He followed a septic course, and sulfa drugs were given. A convulsion apparently occurred the next day, May 5.

The neurologic status was reported on May 9, 1946, and the neurologic interpretation of the findings at that time are correct as far as the guess as to the localization of the lesion is concerned. The expression "hemorrhagic encephalitis" has come to mean a nonspecific reaction in the nervous system that may complicate a febrile illness, specific infections with virus organisms, bacteria, or deficiency status (Wernicke's encephalopathy).

There is also a possibility of hemorrhage in the mesencephalic reticular formation during one of the early convulsions. Spontaneous clearing without sequelae could have occurred. Wernicke's encephalopathy can do the same thing. Also if he only had a suppression of function in this area on a "toxic" basis because of septicemia and fever, this also could clear up.

It therefore appears that proof that this boy's condition was due to poison ivy extract is lacking. It is likely that the seizures were of the so-called febrile convulsions. This implies that he had a lowered convulsive threshold, and the febrile illness was enough to precipitate a seizure owing perhaps to a congenital or acquired defect of the nervous system.

No mention was made in the case history of the subsequent status of the boy's mental development and possible subsequent seizures. Such information would have been helpful in making a more definite decision about the probability of a congenital or acquired defect in the brain.

Rytand[1] reported seven cases in which renal complications appeared as poison oak dermatitis was healing. In one patient, fatal anuria with severe renal tubular degeneration developed. The nephrotic syndrome was prominent in four others; pure lipoid nephrosis seemed a likely diagnosis in three of these patients, chronic glomerulonephritis in one. In two additional cases with suspected and probable streptococcic infection, the syndromes resembled the onset of glomerulonephritis; there was considereble tubular degeneration in one of them. Renal complications became obvious in three days to two months after onset of the dermatitis, usually in one to four weeks. In three patients manifestations of renal disease were coincident with the period of recovery from the dermatitis. Renal complication following poison oak dermatitis may be explained on the basis that (1) broken skin could serve as a port of entry for infection; (2) the agent provoking the dermatitis is one which

causes sensitization. The factor of infection was probably important in production of two cases of streptococcic infection; sensitization probably accounted for the other five.

Movitt [13] reported one case of possible periarteritis nodosa or at least glomerulonephritis in association with the dermatitis of poison oak. Although conclusive and irrefutable proof of the cause-and-effect relationship between the allergen of poison oak on the one hand and periarteritis nodosa on the other is lacking, evidence was presented which strongly suggests this possibility, particularly in view of the well-known sensitizing property of poison oak. The diagnosis of periarteritis nodosa was established only on clinical grounds by Movitt. Pathological confirmation was lacking since two muscle biopsies were reported as showing nothing remarkable. The patient had oral lesions and nonhemolytic and alpha hemolytic Streptococci were isolated from an oral ulcer.

Templeton,[14] Lunsford, and Allington from the same area as Rytand and Movitt hospitalized 106 college students for severe poison oak dermatitis. They found that very little systemic reaction takes place. About four-fifths of the patients reacted with slight fever. About half had a mild leucocytosis, and about half had a moderate eosinophilia. The urine of all 106 patients was normal.

Shaffer,[4] in 1951, reported two cases of acute glomerulonephritis occurring one week and four weeks after injection of Rhus toxicodendron for relief of patients with dermatitis venenata due to poison ivy. One case, that of a 61-year-old man, was fatal. The associated eosinophilia, urticaria, and histological changes in the kidney indicated to Shaffer that the patient's death was the result of an allergic phenomenon. Commenting further on the case, he stated that the evidence that these patients had kidney disease was conclusive. It seemed probable that the kidney disease was due to sensitivity to Rhus toxicodendron. The renal disease in both cases was an acute, rapidly advancing process, rather than a chronic degenerative one as evidenced by the fulminating clinical signs with concomitant laboratory changes. In the fatal case, the eruption was noted to consist of purluent bullae on the feet and a follicular-pustular dermatitis on the trunk. The bacteriologic culture of the bullous fluid was negative for Staphylococcus albus and aureus by the coagulase test. Autopsy was limited to the kidney.

In the cases reported by Rytand and Shaffer, we do not believe that the possibility of pyoderma ‡ has been excluded as a cause for the kidney disease. Necropsy was not done in Rytand's one fatal case and was done only on the kidneys of Shaffer's patient. The possibility of a concomitant unrelated disorder occurring at the time of an ivy dermatitis must be taken into consideration. Ivy poisoning, after all, is a very common disorder, and it is surprising that more cases of ivy dermatitis are not followed by nephritis, pneumonia, coronary occlusion, or a stroke, which was impending when the dermatitis developed.

ANIMAL EXPERIMENTATION

Years ago, McNair,[12] commenting on the pathology of Rhus dermatitis, stated that in severe cases there is albuminuria which may be caused by the partial elimination of these hypothetical poisons by the kidneys. Rhus albuminuria, on the other

‡ References 15, 16, and 17.

hand, may be due to the direct action of lobinol, as it has been found that when Rhus sap has been introduced per os in a rabbit, albuminuria results. Five cubic centimeters of poisonous sap mixed with 15 cc. of cottonseed oil were introduced per os into a rabbit weighing 3,171 gm. A test for albumin in the urine was found to be positive four hours after the poison was introduced. Similarly, Pfaff,[18] in 1897, by the introduction of toxicodendrol per os in a rabbit, said he caused albuminuria. Some animals died shortly after administration of the oil. The autopsies revealed no cause of death.

Our animal experimentation was carried out for the purpose of determining whether or not poison ivy extract is nephrotoxic as suggested by McNair and Pfaff. There is need for a simple method of producing experimental nephritis in animals, so Drs. Fashena and Goth of the Pharmacology Department at Southwestern Medical School carried out these experiments, hoping to be able to use poison ivy extract in the future as a means of producing experimental nephritis. Six rabbits were used.

Rabbit A.—On Dec. 1, 1953, Rabbit A was given intravenously 125 mg. per kilogram of Lederle's concentrated ivy extract, 250 mg. per cubic centimeter, or 25% concentration.‡ Five hours later the rabbit appeared normal. The next morning, however, it was found dead. It had been dead approximately four to eight hours. On gross examination of the animal at necropsy, hemorrhage was noted in the lungs. The kidneys appeared normal, but on section the inner zone of cortex seemed dark. The bladder was filled with urine which on examination was normal. Microscopic study of the kidneys revealed a definite abnormality in the cortex but this represented only postmortem changes.

Rabbit B.—On Dec. 2, 1953, Rabbit B was given intravenously 60 mg. per kilogram of poison ivy extract (Lederle's). This rabbit had been given small doses of poison ivy extract six weeks earlier. Daily 24-hour collections of urine were made for 16 days. The examinations were all negative. On the 16th day, the rabbit was killed with pentobarbital given intravenously. Gross and microscopic examination of the kidneys revealed no abnormality.

Rabbit C.—Rabbit C was given Lederle's concentrated poison ivy extract in October, 1953; 60 mg. per kilogram weight was given intravenously. For 16 days, from Nov. 23 to Dec. 9, daily 24-hour specimens of urine were collected and examined. Urinalyses were all normal. No autopsy was done.

Rabbit D.—Rabbit D was given 75 mg. per kilogram of Lederle's concentrated poison ivy extract intravenously on Jan. 12, 1954. The following day, the animal was found dead. Gross and microscopic examination of the kidneys revealed no abnormalities. The lethal dose of this concentrated extract is apparently just above 60 mg. per kilogram.

Rabbit E.—On Jan. 18, 1954, Rabbit E was given 50 mg. per kilogram of Lederle's concentrated poison ivy extract intravenously. Daily 24-hour collections of urine were taken. No abnormalities in the urinalyses were noted during a 16-day period. The rabbit was killed, and the microscopic studies on the kidneys revealed no abnormalities.

Rabbit F.—On March 6, 1954, Rabbit F was given 60 mg. per kilogram of Lederle's concentrated poison ivy extract intravenously. Daily 24-hour collections of urine were taken. No abnormalities were detected by urinalyses during a 16-day observation period. The rabbit was killed by intravenous injection of pentobarbital. Microscopic study of the kidneys was done, and no abnormality was detected.§

‡ The concentrated poison ivy extract was a special preparation made available by Lederle Laboratories Division, American Cyanamid Company.

§ Dr. E. E. Muirhead, Professor of Pathology at Southwestern Medical School, reviewed the slides on the kidneys of the six rabbits. He reported no evidence of a kidney damage from the ivy injections.

EXPERIMENTATION IN MAN

The foremost authority on poison ivy dermatitis, Dr. Bedford Shelmire,‖ has never observed any serious systemic reactions following uncomplicated dermatitis venenata due to poison ivy or from oral therapy or injections of extract from the plant in his wide experience with plant dermatitis and from giving plant oils orally for hyposensitization. Not one of 20 persons sensitive to poison ivy in the Shelmire [19] experiment on oral hyposensitization—of whom one of us (J. B. H.) was No. 20—developed symptoms of renal irritation. Each volunteer ingested a minimum of 1 oz. (30 cc.) of a 1:25 or 1:10 dilution of poison ivy leaf or root oleoresin in corn oil over a period of a few months.

Mr. H. L. Graham¶ of the Graham Laboratories has been preparing plant extract for contact testing and plant oils for oral treatment since 1939. He has stated that he has never received a complaint or report of nephritis or any systemic reaction from plant extracts used for oral hyposensitization. For the past two to three years urinalysis has been done during the healing phase of all severe or widespread examples of ivy dermatitis. In all, approximately 25 patients, urinalysis has been normal.

Chemically, the dermatitis-producing fraction of poison ivy and other related plants is a phenolic compound.[20] Phenol is capable of being absorbed from the skin in topical remedies and in the proper concentrations can produce kidney damage.[21] In a study on the excretion of poison ivy extract from the body, Dr. Shelmire, who is not allergic to poison ivy, ingested 1 oz. (30 cc.) of a 1:100 extract. No harmful effects were experienced.

Experimentally, Dr. Shelmire [22] gave his nurse the largest single dose and probably the largest quantity ever consumed in the brief period of two and a half months. She took at intervals of three days the following number of capsules each containing 15 drops of a 1:25 dilution # of poison ivy extract: 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 22, 25, 30, 35, 40, 45, 50, and 55.

The only symptoms of intolerance observed during the entire period were transient pruritus ani, dermographism, a mild toxic erythema which appeared about the middle of the treatment stage and disappeared spontaneously after a few days, although oral treatment was not interrupted. During the two and a half months, 6,870 drops—approximately 8½ oz. (255 cc.)—of a 1:25 dilution of the oleoresin was ingested. A routine urinalysis, a complete blood cell count, and blood pressure readings were all normal. A positive patch test reaction was elicited on an ivy-sensitive person with the nurse's blood and urine after the 55 capsules were taken.*

Without doubt, the dose of 55 capsules represented the largest single dose of ivy extract ever taken and the 6,870 drops—or 8½ oz.—the greatest quantity ever taken in a period of two and a half months, yet there were no symptoms of systemic damage in any of the important viscera. Since this nurse was highly allergic to poison ivy, and still is, having experienced ivy dermatitis on numerous occasions, great doubt is cast on the theory that poison ivy extract is capable of causing

‖ Personal communication to the authors.

¶ Personal communication to the authors.

By quantitative skin tests, the extract used was 17 to 600 times as strong as available commercial extracts.

* Shelmire, B.: Personal communication to the authors.

nephritis or the nephrotic syndrome on a sensitization basis. The skeptic may reason that serious systemic toxic effects due to ivy dermatitis or the plant extracts occur only, say, "once in a million times." If that belief were correct, there should be more examples noted than have been reported or experienced.

SUMMARY AND CONCLUSIONS

A review of reports of serious reactions from Rhus toxicodendron is made and evaluated in the light of our present knowledge. Concentrated poison ivy extract is non-nephrotoxic for the rabbit. Two rabbits were given a lethal dose and four rabbits a near-lethal dose of a 25% concentration of poison ivy extract (Lederle's) intravenously. This method is a severe test of a drug or chemical's capacity to cause acute renal damage. Kidney damage was conspicuous by its absence. Daily 24-hour specimens of urine were normal for 16 days after the injections. The animals were then killed, and a biopsy of the kidneys revealed no damage from the extract. Our finding of an absence of a nephrotoxic effect in rabbits is contrary to earlier reports by McNair and Pfaff, who reported Rhus albuminuria in rabbits given an extract of Rhus toxicodendron per os. There is insufficient and inadequate evidence that Rhus dermatitis or extracts administered to ivy-sensitive persons result in systemic injury. Observation of patients given oral extracts of poison ivy for hyposensitization failed to reveal symptoms of renal irritation or symptoms referable to systemic injury. Urinalyses on patients with severe and widespread Rhus dermatitis have all been normal.

A highly allergic ivy-sensitive nurse was given experimentally by Dr. Shelmire most likely the largest single oral dose of ivy extract ever taken and also in 75 days the largest quantity consumed in so brief a time, without symptoms of immediate or delayed toxic damage or systemic sensitization or harm. Secondary infection, which rarely complicates ivy dermatitis, should be anticipated, and specific therapy should be started as soon as the infection is detected. Perhaps infection and not Rhus dermatitis accounts for the rare occurrence of kidney disease seen in association with this common dermatitis.

The subject is open, however, and there is a need for further investigation and study.

ABSTRACT OF DISCUSSION

Dr. Roy L. Kile, Cincinnati: I suppose there are times when all of us are guilty of ignoring the possible systemic effects of cutaneous disease. In a busy practice, one of the easiest errors that can befall us is to regard the skin as a separate and distinct entity.

I think we have all been amazed by the extensive cases of dermatitis venenata that show little in the way of systemic reaction. While I have made no study of the subject—not even a statistical evaluation—it is my general clinical impression that systemic reactions, of any type, with extensive dermatitis venenata from poison ivy are almost nil. At the most, only a fever may be noted, and this will vary, depending on the amount of secondary infection present. I don't remember having seen a case with involvement of the kidneys or any other internal organ. There may be a few isolated cases, but certainly they must be exceedingly rare. In this regard, I would tend to agree with Templeton and co-workers[14] in their studies of 106 college students with severe dermatitis venenata from poison ivy wherein no systemic reactions were observed.

The ingestion or injection of the active principle of Rhus toxicodendron may be a little different matter, though. However, even with this I don't remember having seen any disturbances of internal organs other than the ones which are commonly known to all of us. We have all seen flare-ups of existing dermatitis venenata from the injection of ivy oil; we have seen local reac-

tions at the site of the injection; we have seen pruritus ani and disturbances of the oral mucosa from the ingestion of ivy oil, but I don't ever remember having seen kidney damage from this cause. Animals, particularly sheep, often eat Rhus toxicodendron, with apparently no ill effects. McNair [12] in his book, has an entire chapter devoted to the systemic effects of Rhus toxicodendron. All of these cases, however, were from the ingestion of the berries or leaves of the plant. He describes in great detail the symptoms from the start to their complete recession in a person "poisoned" by ivy. Also in his book are many case histories of such reactions, including some involvement of internal organs and even several deaths. His review of the literature up until 1923, when the book was written, goes back to the early 19th century. There may be doubt about most of the deaths, as has been well pointed out in the paper under discussion. In other words, they may have been caused by secondary infection or concomitant factors other than those produced by the toxic substance in the poison ivy. The infection could cause the kidney damage, as has so well been pointed out by Callaway [17] and his co-workers.

In recent years, particularly in the chemical literature, there have been a number of papers about urushiol. This is the name given to the toxic substance in Rhus toxicodendron. A great deal has been done in regard to its chemistry. Very similar chemical substances are present in both the naturally occurring and synthetic lacquers, as well as the Rhus group of plants. It is hoped that much more experimental work can be done in the future by dermatologists using this purer chemical. Dermatitis venenata as well as toxic systemic reactions could well be restudied using the urushiols if and when they are available.

From the work of Howell and his associates under discussion here today, I believe we could safely say that systemic reactions from the external application of Rhus toxicodendron certainly must be exceedingly rare if they occur at all. Internal ingestion or injection of these substances apparently are not nephrotoxic, and the burden of proof is on the person who attributes the systemic reactions to them. It certainly is a field for further dermatological investigation. We should be very grateful to Dr. Howell and his associates for stimulating us to think of these possible complications.

Dr. James W. Jordon, Buffalo: I am sure we are all grateful to the authors for reassuring us that current methods used in attempts to desensitize or hyposensitize individuals susceptible to dermatitis from the Rhus group of plants is a procedure not likely to produce serious systemic damage to our patients.

Dermatitis venenata due to Rhus toxicodendron is a common condition in our part of the country, and we see many cases of it each summer. In current office practice little attention is paid to the possible systemic effects of this disease. A few severe cases, however, are hospitalized each year where complete physical and laboratory examinations are done. I do not recall a single instance of significant systemic damage among these severe cases where one would expect it, if such damage were prone to occur. One not infrequently sees marked edema of parts of the type commonly seen with any severe dermatitis, but this does not indicate damage to internal structures.

In discussing various internal complications reported associated with poison ivy dermatitis, the authors casually mentioned the possibility of systemic poison due to medications applied or given for the ivy dermatitis rather than from the antigen itself. I believe this point deserves further consideration. The number of medications applied for the relief of poison ivy is legion. As early as 1923, McNair in his monograph listed several pages of drugs or medications employed for the relief of ivy dermatitis. When we remember that mercury, phenol and boric acid all may be absorbed from the skin, particularly where there are numerous areas of dissolution as occurs in ivy dermatitis, and that these drugs may act as systemic poisons, one can readily imagine complications from this source may occur and explain some of the damage to internal structures heretofore reported as being due to ivy poisoning. This is particularly brought to my mind since we recently had a case of phenol poisoning from the too liberal use of phenolated calamine lotion on a patient with extensive ivy dermatitis.

As regards commercial extracts of ivy antigen, I am sure most of us have seen aggravation of signs and symptoms of poison ivy dermatitis following the injection of ivy antigens given in an attempt to alleviate or to shorten the course of this disease. While I have seen many instances of aggravation of poison ivy dermatitis from this source, I have never seen an instance

in which I was convinced that such a procedure produced benefit to the patient although I have not observed damage to internal organs. Fortunately this type of treatment seems to be less commonly used than it has been in the past.

The authors have mentioned animal and human experiments with ivy antigens and noted no severe systemic damage in either from their administration. In my opinion, the best proof that ivy antigen does not produce severe systemic intoxication lies in the clinical observation of hundreds of patients who have taken ivy antigen prophylactically by one means or another. My experience is chiefly limited to the oral administration of the antigen given in gradually increasing doses in an attempt to hyposensitize certain susceptible persons, particularly those who are susceptible to ivy and whose occupations may cause them to contact the plant. The only reactions I have observed among these patients have been dermatological: namely, dermatitis of the fingers or elsewhere from careless contact with the antigen, pruritus ani, or transient generalized erythema. All of these complications may be avoided by proper handling and management of dosage. I am in agreement with the authors that the judicious use of oral extracts of ivy antigen is not fraught with any serious danger to our patients.

Dr. Francis A. Ellis, Baltimore: In 1942 to 1943 (*J. Allergy* **14**:557-563 [Nov.] 1943), when the attempt to desensitize with poison ivy antigen tablets was popular, I attempted to take 0.5 mg. of the antigen and developed pruritus ani and a generalized toxic eruption. In spite of this, I was able to build up my resistance and to take 600 mg. daily of the antigen (in the dry form) without any difficulty. According to my figures, the maximum dose taken by Dr. Howell's patient, on the average, was 150 mg. a day. In my case with 600 mg. a day, there were no systemic symptoms whatsoever, and repeated urine examinations and other tests have all been negative.

The important lesson from our experiment was that even with this dose, over a period of months, we did not cause temporary or permanent desensitization; in fact, I still give a positive reaction to a patch test with a 1 to 100 extract that lasts for several weeks. Two years after the original experiment, when I took a 25 mg. tablet, I again developed generalized itching and pruritus ani. These were the original tablets, and they may have deteriorated somewhat.

Dr. Arthur C. Curtis, Ann Arbor, Mich.: I enjoyed Dr. Howell's paper immensely, and I can assure you that in rabbits and one nurse, he has convinced me that Rhus toxicodendron is not a nephrotoxic substance.

I am familiar with the work of Rytand and Lowenburg and Shaffer, which the authors have cited. Their reports on the development of periarteritis nodosa, poisoning, and glomerular nephritis are not well substantiated. In those instances in which periarteritis nodosa occurred, a drug used in the treatment of the skin infection might have caused the disease. Certainly a bacterial infection of the skin in the patients who have ivy dermatitis can be the etiologic factor of the nephritis that follows (Callaway, J. L., and O'Rear, H. B.: Pyogenic Infections of Skin: Etiologic Factor in Acute Glomerulonephritis of Children, A. M. A. Arch. Dermat. & Syph. **64**:159 [Aug.] 1951).

Dr. Marion B. Sulzberger, New York: I am grateful to Dr. Howell, and I also want to commend the discussers of this paper on what they have said. I think this is an important subject, and I should like particularly to emphasize Dr. Jordon's remarks concerning the exacerbations of active cases of poison ivy following the injections of the generally available, purchasable specific extracts, when these are given therapeutically while lesions are present. For the flaring up of quiescent lesions—and even the reactivation of old lesions which are no longer visible—occurs so regularly following these injections and the therapeutic effectiveness of these treatments is so questionable that I think it is a procedure that should be condemned and abandoned.

Regarding the main thesis of Dr. Howell's paper, we have examined the urines and blood pressures and done other simple clinical tests for kidney function on our patients with severe poison ivy dermatitis ever since the question of possible kidney damage has been bruited about. Just like Dr. Howell, we have not discovered in any of our cases any such kidney damage that could be attributed to the dermatitis.

Dr. J. B. Howell, Dallas, Texas: I would like to thank Drs. Kile, Jordon, Ellis, Sulzberger, and Curtis for their discussion.

The rabbit is the usual laboratory animal used by the pharmacologists for the evaluation of acute nephrotoxic properties of medications such as polymyxin, bacitracin, and others. Since the rabbits were not allergic to poison ivy (perhaps they are incapable of being sensitized), we can state only that lethal and near-lethal doses of concentrated ivy extract given intravenously did not have a nephrotoxic effect.

In answer to Dr. Kile's question, I would say we did not attempt to determine the cause of death in the two rabbits that we killed, and the pathologist examined only the kidneys. McNair stated that he was unable to determine the cause of death in the rabbits that died after his experimental administration of Rhus sap in an oily suspension per os.

It was a great disappointment to us that we failed to sensitize hogs and/or guinea pigs experimentally to poison ivy. For three months one of our technicians applied a very concentrated acetone dilution of poison ivy extract furnished us by the Graham Laboratories to a large area of the right side of six young hogs from three to seven times weekly. We hoped to sensitize the hogs and then to give a sizable quantity of poison ivy extract (Lederle) intravenously to the animals. After a period of a few weeks, to allow for a possible incubation period of sensitization of the kidneys, we planned to kill the animals and study the kidneys histologically for evidence of nephritis on an allergic basis. We realize, therefore, that there is this missing link of information on the subject.

We believe, however, that the experiments of Shelmire and the experience of dermatologists throughout the country point to the fact that uncomplicated ivy dermatitis and the administration of extracts of the plant are not followed by systemic injury.

REFERENCES

1. Rytand, D. A.: Fatal Anuria, Nephrotic Syndrome, and Glomerular Nephritis as Sequels of the Dermatitis of Poison Oak, Am. J. Med. **5**:548 (Oct.) 1948.

2. Rytand, D. A.; Burnham, DeW. K., and Cox, A. J.: Periarteritis Nodosa Following Dermatitis of Poison Oak and Primrose, Stanford M. Bull. **6**:319 (May) 1948.

3. Lowenburg, H.: Poisoning Due to Tincture of Rhus Toxicodendron, J. A. M. A. **135**:91 (Sept. 13) 1947.

4. Shaffer, B.; Burgoon, C. F., and Grosman, J. H.: Acute Glomerular Nephritis Following Administration of Rhus Toxicodendron: Report of a Fatal and Near-Fatal Case, J. A. M. A. **146**:1570 (Aug. 25) 1951.

5. Anonymous: Medical Notes: Death from Ivy Poisoning, Boston M. & S. J. **137**:302, 1897.

6. Barnett, H. L.; Simons, D. J., and Wells, R. E. Jr.: Nephrotic Syndrome Occurring During Tridione Therapy, Am. J. Med. **4**:760 (May) 1948.

7. Wren, J. C., and Nutt, R. L.: Nephrotic Syndrome Occurring During Paramethadione Therapy: Report of a Case with Clinical Remission, J. A. M. A. **153**:918 (Nov. 7) 1953.

8. Anonymous: Poisoning by an Infusion of Poison Oak, West. J. Med. & Surg. **2**:364 (Oct.) 1848.

9. Moorman, J. W.: Poisoning by Eating the Fruit of the Rhus Toxicodendron, Am. J. M. Sc. **51**:560 (May) 1866.

10. Stokes, J.: Peculiar Cases of Poisoning from the Root of the Rhus Toxicodendron, Med. & Surg. Reporter **17**:373 (Nov. 2) 1867.

11. Alumbaugh, W. E.: Fatal Results from Chewing Leaves of the Poison Oak Plant, Med. World **5**:176, 1903.

12. McNair, J. B.: Rhus Dermatitis: Its Pathology and Chemistry, Chicago, University of Chicago Press, 1923.

13. Movitt, E. R.; Mackenbrock, F. C., and Clement, C. E.: Periarteritis Nodosa; Antigens of Trichinella Spiralis and Poison Oak as Exciting Causes, Stanford M. Bull. **8**:59 (May) 1950.

14. Templeton, H. J.; Lunsford, C. J., and Allington, H. V.: Poison Oak Dermatitis; Hematologic, Urinary, and Temperature Changes, J. Invest. Dermat. **8**:53 (Nov.) 1947.

15. Futcher, P. H.: Glomerular Nephritis Following Infections of the Skin, Arch. Int. Med. **65**:1192 (June) 1940.

16. McCullough, G. C.; Coffee, J. Y.; Trice, P. A., Jr.; Stone, J. J., and Crandall, H. L.: Acute Glomerulonephritis: Impetigo as Etiologic Factor, J. Pediat. **38**:346 (March) 1951.

17. Callaway, J. L., and O'Rear, H. B.: Pyogenic Infections of Skin: Etiologic Factor in Acute Glomerulonephritis of Children, A. M. A. Arch. Dermat. & Syph. **64**:159 (Aug.) 1951.

18. Pfaff, F.: Active Principle of Rhus Toxicodendron and Rhus Venenata, J. Exper. Med. **2**:181 (June) 1897.

19. Shelmire, B.: Hyposensitization to Poison Ivy, Arch. Dermat. & Syph. **44**:983 (Dec.) 1941.

20. Wasserman, D., and Dawson, C. R.: The Toxic Principle of Poison Ivy and Other Related Plants, J. Chem. Ed. **20**:448 (Dec.) 1943.

21. Cronin, T. D., and Brauer, R. O.: Death Due to Phenol Contained in Foille®: Report of a Case, J. A. M. A. **139**:777 (March 19) 1949.

22. Shelmire, B.: Cutaneous and Systemic Reactions Observed During Oral Poison Ivy Therapy, J. Allergy **12**:252 (March) 1941.

HISTOPATHOLOGIC CORRELATION OF LESIONS OF PAPULAR URTICARIA AND POSITIVE SKIN TEST REACTIONS TO INSECT ANTIGENS

BERTRAM SHAFFER, M.D.
COLEMAN JACOBSON, M.D.
AND
HERMAN BEERMAN, M.D.
PHILADELPHIA

A SUBSTANTIAL body of evidence indicates that many cases of papular urticaria are related to insect bite sensitivity.* This opinion is based, in part, on the fact that the patients with papular urticaria give positive delayed (tuberculin type) skin test reactions to the intradermal injection of insect antigen. (Figs. 1, 2, and 3).

In an effort to determine the validity of this etiologic concept, we have examined a number of lesions of papular urticaria histologically and have compared these findings with those of positive urticarial and delayed tuberculin-type skin reactions to insect antigen, and with ordinary insect bites. These studies have shown a striking similarity of such lesions.

METHOD OF STUDY

Patients with papular urticaria were given intracutaneous injections of mosquito (Culex pipiens) flea, (Ctenocephalides felis), and bedbug (Cimex lectularius) antigens. These antigens were prepared after the method of Cherney and co-workers [14]; 0.1 cc. of 1:5,000 solution of each antigen was injected intradermally into the skin of the upper extremity. Readings were made at 30 minutes and at 48 to 72 hours. As a control, 0.15% phenol in saline solution was also injected.

The following specimens were examined histologically:

1. One early (urticarial) lesion from papular urticaria.
2. Four late (papular) lesions from papular urticaria.
3. Two immediate (urticarial—30 minute) reactions to insect antigen (flea) taken from patients with papular urticaria.
4. Eight delayed (tuberculin type—48 to 72 hours) reactions to insect antigen (five mosquito, two Cimex, one flea) taken from patients with papular urticaria.
5. Two ordinary insect bites in "normal" subjects. These bites were of several hours' duration.

Adapted from a paper given before the American Academy of Dermatology and Syphilology, Chicago, Dec. 9, 1953.

From the University of Pennsylvania, Departments of Dermatology, School of Medicine and Graduate School of Medicine.

* References 1 to 13.

The main histologic findings in most of these lesions showed a moderate to heavy perivascular and periappendiceal infiltrate (chiefly about the sweat glands) consisting of lymphocytes and large numbers of eosinophiles. In some instances, neutrophiles were also found. The infiltrate was disposed chiefly in the middle and lower thirds of the corium and in many instances involved the panniculus itself. There were variations in acuteness and destructiveness of the process, as indicated in several cases by edema, dilatation of the blood vessels, and focal necrobiosis in the lower third of the corium.

Fig. 1.—A. G., aged 4, showing numerous papular lesions of papular urticaria, some of which are excoriated. The distribution on the exposed surfaces is typical. (Black and white print from a kodochrome by Dr. Jack Weiner.)

Fig. 2.—Numerous papular, crusted and excoriated lesions on the knees and thighs of P. D., a Negro child, aged 2 years.

The changes in the epidermis appeared to be merely incidental and, in general, varied from normal findings to mild acanthosis with slight to moderate parakeratosis. On occasion, edema and superficial ulceration with crusting was found.

In general, the immediate 30-minute reaction tests to insect antigen, the true insect bites, and the early lesion of papular urticaria had more in common histologically, while the delayed (48 to 72 hour) test reactions resembled more closely the papular lesions of papular urticaria.

In the first group, interstitial edema, sparse to moderate infiltrate, and predominance of eosinophiles were the features that dominated the histologic picture.

In the second group, the changes in the corium were of two types. The positive delayed skin reactions and the inflammatory papular lesions of papular urticaria were featured by the denseness and extensiveness of the infiltrate and the conspicuous presence of eosinophiles. Edema was not apt to be present, but at times focal necrobiosis in the corium seemed to replace this feature. On the other hand, the old involuting papular lesions of papular urticaria were marked by relative sparseness of infiltrate and absence of eosinophiles, the cellular collections in these cases being comprised solely of lymphocytes.

Fig. 3.—Results of skin testing with insect antigens in case P. D. (Fig. 2). No. 1, Positive 48-hour test to flea antigen; No. 2, negative test bedbug (cimex) antigen, and No. 3, negative test—control solution.

COMMENT

Goldman, Rockwell, and Richfield[15] have reviewed the literature and have described the histopathology of the bites of arthropods. They remark on the heaviness of the infiltrate and the presence of eosinophiles. Although they point out that in the early or urticarial phase in nonsensitive persons the infiltrate consists largely of neutrophiles, they do emphasize that in allergic persons the presence of eosinophilia appears much earlier than it does in nonsensitized subjects. This seems to conform to our findings, inasmuch as we consider patients with papular urticaria to be persons who are sensitized to the bites of insects. In this connection it must be

pointed out that we are not dealing with those chronic reactions simulating granulomas and lymphoblastomas described by Ash and Spitz,[16] Allen,[17] and Winer and Strakosch.[18]

In previous studies † we attempted to show that most cases of papular urticaria were associated with sensitization to insect bites of the tuberculin type and we proposed a dynamic explanation of the allergic mechanism involved.[3] It seemed that papular urticaria represented the earliest (i. e., the tuberculin) allergic phase in the development cycle of insect allergy. In the average person this stage is transient and unimportant, but in the patient with papular urticaria this tuberculin phase is prolonged and intense, and only after several years does the kind of desensitization develop that leads subsequently to the appearance of the urticarial phase ordinarily identified with the clinical picture of insect bites.

A therapeutic regimen aimed at eliminating insects resulted in the prompt eradication of the disease in the great majority of cases and has in the last several years greatly reduced papular urticaria as a chronic problem in our clinics. This treatment consisted of the use of 5% chlorophenothane (D. D. T.) dusting powder topically, the spraying of the household with a solution of chlorophenothane in a kerosene base, and also the elimination of contacts with cats and dogs infested with fleas.

Recently Rook and Frain-Bell [19] have confirmed our therapeutic findings and on the basis of the fundamental work of Mellanby have supported our concept of the pathogenesis of this disease.

In previous publications we had pointed out that papular urticaria (lichen urticatus) is a clinical syndrome consisting of numerous closely set wheals and papules. In our experience the papules rather than the urticarial lesions always dominate the clinical picture. The lesions are disposed mainly on the exposed portions of the body. The eruption occurs chiefly in children between the ages of 2 and 7 years. Its incidence is highest among patients of the lower economic strata and it develops most frequently in the hot weather months. Because the eruption gives rise to excruciating pruritus, the lesions are frequently excoriated and secondarily impetiginized.

Criticism had been leveled against the insect etiology of papular urticaria, particularly in regard to diagnosis.[19] It was claimed that all cases of "papular urticaria" responding to an anti-insect regime are not in reality papular urticaria but merely insect bites that look like papular urticaria. This seems to us to be begging the question. It is like saying that all cases of urticaria are urticaria except those that are caused by penicillin. The differential diagnosis of papular urticaria is an easy one; in the majority of cases the disease is unmistakable, and its identity is easily made by an experienced dermatologist, particularly if he works in a large children's clinic in the poorer section of a large city. If one carefully follows the description of Bateman,[20] who originally described this disease, and diagnoses only those cases as papular urticaria that conform to his description, we do not feel that one will be disappointed in his therapeutic results, if properly and carefully applied against insects.

† References 1 and 2.

SUMMARY AND CONCLUSIONS

Lesions from patients with papular urticaria, positive skin test reactions to mosquito, bedbug and flea antigens in patients with papular urticaria, and ordinary insect bites were examined histologically.

The early or urticarial type lesion of papular urticaria, the early or urticarial type skin test response to the intradermal injection of insect antigen, and the ordinary insect bite presented many features in common, namely, the presence of edema and a dense perivascular and periappendiceal infiltrate in the middle and the lower thirds of the corium consisting mainly of lymphocytes and eosinophiles.

The late or papular lesions of papular urticaria appeared to fall into two groups: 1. Those of the inflammatory variety resembled histologically very closely the late or tuberculin type reaction to the intradermal injection of insect antigen in that there was a dense perivascular and periappendiceal infiltrate of lymphocytes and eosinophiles in the middle and lower two-thirds of the corium. Here, however, edema was not apt to be present but in its place focal necrobiosis was found at times. 2. The subsiding noninflammatory late papular lesions of papular urticaria showed also a perivascular and periappendiceal infiltrate in the middle and lower two-thirds of the corium but in this case the infiltrate was apt to be sparse and to consist almost solely of lymphocytes. In the case of all late papular lesions of papular urticaria the epidermal changes consisted of moderate acanthosis and hyperkeratosis with an occasional specimen showing ulceration and crusting.

We feel that these histologic findings add some support to the concept that papular urticaria is often an allergic disease induced by the bites of insects.

REFERENCES

1. Shaffer, B.; Spencer, M. C., and Blank, H.: Papular Urticaria: Its Response to Treatment with DDT and the Role of Insect Bites in Its Etiology, J. Invest. Dermat. **2**:293, 1948.

2. Blank, H.; Shaffer, B.; Spencer, M. C., and March, W. C.: Papular Urticaria; Study of the Role of Insect in Its Etiology and the Use of DDT in Its Treatment, Pediatrics **5**:408, 1950.

3. Shaffer, B.; Jacobson, C., and Beerman, H.: Papular Urticaria, Its Relationship to Insect Allergy, Ann. Allergy **10**:411, 1952.

4. Chipman, E. D.: Urticaria, with Special Reference to the Cause in Papular Forms of Children, California Med. **8**:207, 1910.

5. Dietrich, A.: Hautreaktionen nach Ungezieferbissen, Monatsschr. Kinderh. **75**:70, 1938.

6. Dietrich, A.: Hautreaktionen nach Ungezieferstichen unter dem Bild eines Lichen urticatus, Arch. Dermat. u. Syph. **182**:668, 1942.

7. Hamburger, F.: Lichen urticatus durch Ungeziefer: Reply to Pfaundler, Munchen. med. Wchnschr. **89**:652, 1942.

8. Lunsford, C. J.: Flea Problem in California, Arch. Dermat. & Syph. **60**:1184, 1949.

9. Goldman, L.: Lichen Urticatus Syndrome as a Manifestation of Sensitivity to Bites from Various Species of Anthropods, Arch. Dermat. & Syph., **58**:74, 1948.

10. Bowen, R.: Insects and Allergic Problems, South. M. J. **44**:838, 1951.

11. Fuchs, H.: Urticaria papulosa durch Stiche von Scleroderma domestica, Dermatologica **105**:213, 1952.

12. Harant, H., and Huttel, W.: Un insecte vulnérant peu connu, Bull. Soc. path. exot. **43**:449, 1950.

13. Rook, A., and Frain-Bell, W.: Papular Urticaria, Arch. Dis. Childhood **28**:304, 1953.

14. Cherney, L. S.; Wheeler, C. M., and Reed, A. C.: Flea Antigen in Prevention of Flea Bites, Am. J. Trop. Med. **19**:327, 1939.

15. Goldman, L.; Rockwell, E., and Richfield, D. F.: III. Histopathological Studies on Cutaneous Reactions to Bites of Various Arthropods, Am. J. Trop. Med. **1**:514, 1952.

16. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, W. B. Saunders Company, 1945, p. 325.

17. Allen, A. C.: Persistent "Insect Bites" (Dermal Eosinophilic Granulomas) Simulating Lymphoblastomas, Histiocytes, and Squamous Cell Carcinoma, Am. J. Path. **24**:367, 1948.

18. Winer, L. H., and Strakosch, E. A.: Tick Bites—Dermacentor variabilis (Say), J. Invest. Dermat. **4**:249, 1941.

19. Sulzberger, M. B., and Baer, R. L.: Editorial Comment, in Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1949, p. 44.

20. Bateman, T.: A Practical Synopsis of Cutaneous Diseases: Second American Edition, Philadelphia, James Crissy, 1824.

RELATIONSHIP BETWEEN RITTER'S AND LEINER'S DISEASES

HAROLD N. COLE Jr., M.D.
RICHARD G. HODGES, M.D.
AND
FRANCIS F. SILVER, M.D.
CLEVELAND

EUROPEAN authors favor the concept that Ritter's and Leiner's disease are separate and distinct entities, whereas many American authors have expressed the opinion that the latter is simply a variant of the former condition.

In 1878, von Rittershain [1] described an exfoliative disease of the skin in nursing infants which commenced as a single, red, exfoliating plaque, which usually would appear over the lower half of the face. This primary lesion would then spread rapidly until the entire skin surface was involved. Often this would include the conjunctivae and mucous membranes of the mouth and nose as well. In addition to the exfoliation, vesicles and bullae would appear. Beneath the exfoliating portion, the surface was generally moist, weeping and crusted, although in some instances it was dry, red, and brawny in character. A positive Nikolsky sign could invariably be elicited early in the course of the disease. As a rule, the condition appeared between the second and fifth weeks of life. The mortality rate was 50%.

In 1907, Carl Leiner,[2] of Vienna, described a series of cases of generalized exfoliative dermatitis occurring in newborn and older infants which often terminated fatally, particularly in those who had been breast fed.[3]

It usually appeared first on the scalp and face, and for a period would simulate an infantile or seborrheic eczema. In other instances, it would develop first on the buttocks and gluteal folds as a dry, reddened, infiltrated, desquamating area. The desquamation varied from fine scales to large dry flakes or even a greasy, seborrheic variety.

There was considerable variation as to the extent of infiltration in the skin. Whereas the erythroderma was generally of the dry type, the moist variety would sometimes supervene. In some instances, the whole integument would become involved within a few days. In others, many weeks would elapse before the process became universal.

Sano [4] has pointed out that in Leiner's disease, the skin is inflamed but not ulcerated, and that seborrhea of the scalp is characteristic. Also, Nikolsky's sign is absent.

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From the Departments of Dermatology and Syphilology, and of Pediatrics, St. Luke's Hospital, and from the Department of Dermatology and Syphilology, Western Reserve University, School of Medicine, and University Hospitals.

PATHOLOGY

Weidman and Gilman [5] stress the following changes in a study of two cases of Ritter's disease:

Skin—hypoplasia of the epidermis; parakeratosis and acanthosis in some areas, and complete separation of the epidermis in others; capillary dilatation, particularly in the subpapillary portion of the corium. Many capillaries were observed in one case to be filled with thrombi consisting of fibrin and clumps of bacteria (staphylococci). The authors were impressed by the paucity of inflammatory infiltrate.

Thymus—hyperplasia in one case.

Heart—cloudy swelling; hyperplasia of connective tissue fibers.

Lungs—passive congestion.

Liver—chronic passive congestion.

Stomach—local subacute ulceration.

Kidneys—cloudy swelling.

Adrenals—lipoid hypoplasia.

Pancreas, colon, spleen, mesenteric lymph nodes—diffuse fibrosis. Abundant deposits of hemosiderin were observed in the lungs, liver, and spleen in conjunction with the passive congestion. There was hypoplasia of lymphoid tissue in general.

There are marked discrepancies as to the histopathology of the skin. A case with a positive Nikolsky sign may show marked inflammatory cell infiltration in the skin, although these inflammatory cells are presumably not characteristic of Ritter's disease.* In Leiner's disease, in which the cellular infiltrate should be abundant, it may be so scanty as to be almost negligible.[4]

A characteristic of Ritter's disease is said to be separation of the stratum granulosum.†

In Leiner's disease, acute congestion associated with catarrhal changes in the intestinal mucosa is a consistent finding.[4]

Cases of Ritter's disease reported by Lee and colleagues,[11] and Widerman,[12] showed essentially the same features anatomically and histologically as described by Weidman and Gilman.

Skin cultures were positive for hemolytic Staphylococcus aureus in three of Lee's cases, and two of four cases in which autopsy was done showed fatty degeneration of the liver.

In addition to the material from Weidman and Gilman's cases, the opportunity has been afforded us to study histologic sections of the skin, from two cases of Ritter's disease in white infants, 7 and 17 days of age, by Dr. Wolf W. Zuelzer, Pathologist and Director of Laboratories, Children's Hospital of Michigan, Detroit.*

Parakeratosis, areas of separation of the stratum corneum from the stratum malpighii, and areas of separation of the epidermis within the prickle cell layer itself were observed. Capillary dilatation, particularly in the subpapillary portion of the corium, was a common feature, much more pronounced in one case than

* References 6 and 7.

† References 8, 9, and 10.

* Zuelzer, W. W.: Personal communication to the authors.

in the other. There was a moderate inflammatory infiltrate of polymorphonuclear leucocytes present in one. In the case which showed pronounced capillary dilatation, there was almost complete absence of any infiltrate.

In a survey of three Cleveland hospitals (Saint Luke's Babies and Children's, Division of University Hospitals, and Cleveland City), 12 cases were found in which a final diagnosis of Ritter's or Leiner's disease was made, since 1938. Of these, four patients died while the remaining eight ultimately recovered. The following case came to autopsy:

D. O., a 5-day-old white girl, was admitted to Cleveland City Hospital on July 14, 1941, because of convulsive rigors, vomiting, and peeling of large areas of skin. The mother was known to have had congenital syphilis. At birth the infant appeared cyanotic, dehydrated, and unusually quiet. On hospital admission, large areas of redness and exfoliation were noted over the right side of the face and buttocks. The eyes were observed to roll downward in a jerking motion, and

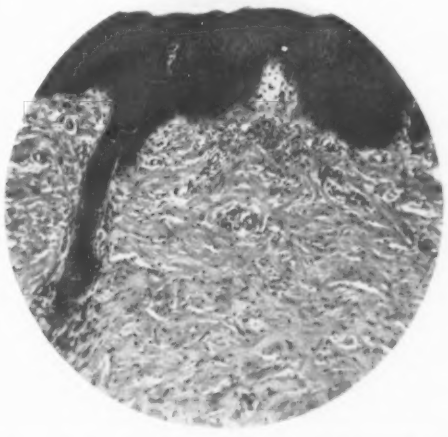

Fig. 1.—Leiner's disease. Note prominent parakeratosis and acanthosis, edema of the papillae, capillary dilatation, and moderate polymorphonuclear leucocytic infiltrate; × 10.

there were occasional convulsive twitchings of the arms and shoulders. Spinal fluid was bloody, but it did not appear to be under increased pressure. Culture yielded no organisms from either the spinal fluid or the blood. The infant died on July 15, 1941.

Clinical Diagnosis: Ritter's disease.

Anatomical Diagnosis: Focal hemorrhages of the lungs; partial bilateral atelectasis; extensive bilateral acute nephrosis; severe fatty metamorphosis of the liver; passive hyperemia of spleen, kidneys, stomach.

Microscopic sections of skin were obtained from the following case of Leiner's disease:

J. K., a 6-week-old white girl was admitted to Saint Luke's Hospital on Jan. 19, 1954 because of a skin rash. She was born in this hospital weighing 5 lb. 7 oz. (2,466.4 gm.) and appears to have done well for the first three weeks of life. At that time, small whitish lesions broke out over the chest and back. These were treated with baby oil and corn starch. In spite of this treatment, the skin lesions spread and became red and scaly. On admission almost the entire integument was involved. The infant had been eating well and had continued to gain weight. At

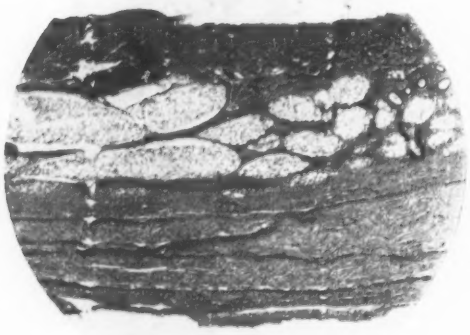

Fig. 2.—Ritter's disease. Note hypoplasia of epidermis and point of complete separation of epidermis, capillary dilatation, and almost complete absence of inflammatory infiltrate; ×10. (Courtesy of Dr. Wolf W. Zuelzer, Department of Pathology, Children's Hospital of Michigan, Detroit.)

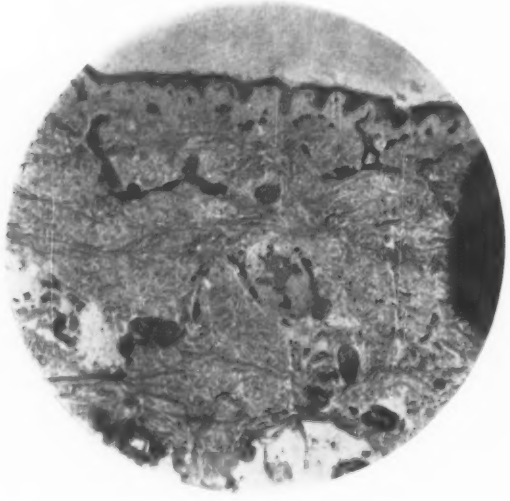

Fig. 3.—Ritter's disease. Note separation of stratum corneum, capillary dilatation, and paucity of inflammatory infiltrate. (Courtesy of Dr. Wolf W. Zuelzer, Department of Pathology, Children's Hospital of Michigan, Detroit.)

no time was she feverish. Her past and family history was not remarkable. She had been artificially fed from time of birth and had been receiving a preparation containing vitamins A, C, and D (Tri-Vi-Sol).

Admission temperature was 99.5 F. (37.5 C.). Positive findings were limited to the skin, which showed a diffuse erythematous scaly rash which was generalized. Marked seborrheic dermatitis was present on the scalp. Two small bullous lesions were present on the anterior chest. Hemogram elicited Hb. 18.3 gm., white blood cells 9,000, with a normal differential. Urogram was negative. The baby was given an antibiotic, and supplementary vitamin B complex was added. Local therapy consisted of 2% salicylic acid ointment, which on the fourth hospital day was changed to plain liquid petrolatum. During her hospital stay, there was a considerable degree of improvement and she was discharged on Jan. 29, 1954.

Histologic sections of skin showed parakeratosis and acanthosis; considerable edema of the papillae and throughout the subpapillary portion of the corium; capillary dilatation particularly in the upper corium; moderate inflammatory infiltrate of polymorphonuclear leucocytes, but not so marked as one would anticipate from the degree of erythema, scaling, and infiltration of the skin clinically. The deeper corium showed no changes.

Except for more of a tendency toward hypoplasia of the epidermis in Ritter's and more prominent parakeratosis and acanthosis in Leiner's disease, sections of these two conditions would otherwise appear to be indistinguishable. As might be expected, capillary dilatation is more pronounced in the more acute Ritter's disease.

COMMENT

Ritter [1] believed the condition that he described to be pyogenic in origin.

Leiner [2] felt that the skin reaction was of the nature of a toxic response to pathogens generated in the gastrointestinal tract.

Lee and co-workers [11] reported a biphasic outbreak of impetigo neonatorum and dermatitis exfoliative neonatorum, with 12 cases of impetigo and 10 cases of Ritter's disease. Their evidence suggested that hemolytic Staphylococcus aureus was causative.

A similar epidemic which developed in a newborn nursery was reported by Govan and co-workers.[13] Of 80 infants exposed during a four-week period, 16 showed some manifestation of staphylococcal infection of the skin, while 4 developed Ritter's disease.

Widerman,[12] Kendall, and Aegerter,[5] and Schlesinger [14] thought that in addition to the infectious element, there was a fundamental deficiency or defect of the skin and mucous membranes.

Sano's case,[4] a 17-day-old infant, showed a hypocalcemia which he felt was indirectly responsible for the disease. He hypothesized that this resulted in intestinal dysfunction which interfered with vitamin absorption, which in turn made the infant more prone to infection.

A case of Ritter's disease with apparent disturbance of lipoid metabolism was described by Caillíau and Fleury.[6] Curious xanthomatoid cells were found deep in the skin, in lymph nodes, and in the lungs.

Wiener [16] reported the occurrence of Ritter's disease in premature twin boys. The mother gave a history of severe and extensive Rhus dermatitis near term. He proposed that the toxic principle of the plant combined with the mother's skin proteins and altered them sufficiently to make them antigenic, thus stimulating the production of antibodies. He hypothesized that these antibodies could have passed through the placenta into the bodies of the twins and produced the dermatitis.

Reports of Ritter's disease occurring concurrently with bullous staphylococcic impetigo in epidemic form and the frequent finding of staphylococci on skin culture favor the hypothesis that a basic etiologic factor in this disease is staphylococcic infection of the skin.

The majority of cases, however, are reported as single isolated examples. This suggests the presence of some additional factor which markedly diminishes the resistance of certain infants, making them more prone to a virulent, rapidly spreading skin infection and systemic toxemia.

That this factor is an inherent defect in the skin seems unlikely, as patients have recovered in whom no defect or abnormality of the skin could be found.

Efforts to disclose any consistent endocrine changes have not been fruitful.

The possibility of a nutritional deficiency seems more plausible. The incidence of the disease in breast-fed infants appears to be more than coincidental.

In support of this view, Svejcar and Homolka [16] point out a significant increase in the incidence of Leiner's disease in Prague, following both the first and second World Wars, at a time when the dietary restrictions of the general populace would be foremost. These same authors claimed a striking reduction in the mortality of this disease in 1948, with the institution of biotin therapy.

Whereas Ritter's disease is generally regarded as being more malignant and fulminating, occurring within the first few weeks of life, characterized by the formation of bullae, areas of denudation, and a positive Nikolsky sign, and Leiner's disease is thought to appear somewhat later, to be less often fatal, characterized by an essentially dry exfoliation, there remains little else clinically or histologically to distinguish between the two.

It seems more likely that Leiner's disease is simply a variant occurring in an infant who possesses a relatively greater degree of resistance, which results in a somewhat modified, subacute form of Ritter's disease.

On this premise, therapy in either clinical picture should consist of prompt institution of an antibiotic to combat the infectious element, and supplementary vitamin B, in the hope of supplying whatever factor may be lacking in the metabolic demands of the infant.

SUMMARY AND CONCLUSIONS

A review of the clinical features of Ritter's and Leiner's disease is presented.

Necropsy findings in one case of Ritter's disease, and cutaneous histologic changes in two cases of Ritter's disease and one case of Leiner's disease are discussed.

Because of the close clinical similarity and lack of distinguishing histological characteristics, it is felt that Leiner's disease probably represents a modified, subacute form of Ritter's disease.

The etiologic basis of the condition appears to be staphylococcal infection in a patient whose susceptibility has been increased by the lack of an essential nutritive factor. Some evidence indicates that this factor may be one or more components of the vitamin B complex.

Treatment should include prompt institution of an antibiotic and supplemental vitamin B complex.

ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: It is often rewarding to review old ideas in the light of new knowledge and to reevaluate established doctrines by the application of modern concepts and techniques.

I for one feel quite certain that Dr. Cole has done Dermatology a service by presenting this critical review of the resemblances and differences between Leiner's erythroderma and Ritter von Ritterhain's dermatitis exfoliativa. Like most dermatologists and pediatricians of our day, I have always accepted the doctrine that these diseases of infancy are quite distinct and different from one another. In the accompanying Table, I have attempted to list some of the principal features which are generally regarded as differentiating Ritter's dermatitis from Leiner's erythroderma.

Despite such very apparent differences, it is still conceivable that additional studies into mechanisms, into pathogenesis and etiology, might bring to light facts which would tend to support Dr. Cole's thesis that these diseases may be more closely related than our present knowledge permits us to assume. For it is incontrovertible that all kinds of studies into these diseases are now urgently required. It would, for example, be of value to know whether cytodiagnostic smears and histopathologic examinations of Ritter's disease would reveal acantholytic cells and acantholytic bullae and epidermal fissures while similar examinations of Leiner's disease would

Features Differentiating Dermatitis Neonatorum from Erythroderma Desquamativa

	Dermatitis Neonatorum Exfoliative (1878)	Erythroderma Desquamativa (1907)
Age of Onset	2 to 5 Days	20 to 60 Days
Course	Acute, usually few weeks	More chronic, usually months
Outcome	90% (?) fatal before modern antibacterials	Lower mortality (30% to 80% (?))
Epidemiology	Endemics (with impetigo, P. infectiosus)	Almost exclusively breast-fed infants; nutritional deficiencies (?)
Bullae	Common	Absent
Epidermolysis	Nikolsky—characteristic	Absent
Other clinical features	"Scalded" appearance; red moist areas	Greasy scales; "cradle-cap"; diarrhea, G.-I. inflammation
Response to therapy	Modern antibacterials reported effective	Casein, raw liver; low-fat sometimes effective (L. W. I.

not. It would also be most instructive to ascertain whether Leiner's disease had distinct familial associations with seborrhea, seborrheic dermatiits, acne, and baldness in parents, siblings and other blood relatives, and whether infants recovered from Leiner's disease themselves later develop classic seborrheic states, while these individual and familial seborrheic findings were not regularly encountered in those affected by Ritter's disease. Similarly, as once suggested by Lewis Webb Hill, it should prove instructive to discover how often Leiner's disease was accompanied by urticarial reactions to skin tests and passive transfer antibodies to so-called "protein" allergens, together with other stigmata of atopy in the infant and/or his family and how often these atopic associations were present or absent in Ritter's dermatitis.

As far as I know, there is also a lack of accurate information in regard to the results of modern microbiological studies of the skin lesions, and the findings with newer dermatohistochemical and biochemical techniques, to name but a few of the gaps in our present knowledge.

These and many other studies may not have been feasible until very recently because of the high and rapid mortality in Ritter's dermatitis and the relatively low recovery rate in Leiner's erythroderma. But with modern therapy, the improved recovery rates in both of these infantile dermatoses should permit not only the just-mentioned sorts of investigations but also systematic studies of the comparative effectiveness of different kinds of therapy. Thus the statistical data on the relative responsiveness of typical cases of Leiner's disease and of Ritter's disease to such therapeutic weapons as the modern antibacterials and other anti-infective agents (e. g. antibiotics, sulfapyridine, quinones, stilbamidines); the modern vitamin preparations (B_{12} and nicotinic acid derivatives, etc.); the modern endocrinologic derivatives (corticotropin [ACTH], cortisone, and hydrocortisone) might help to establish possible similarities and differences and also advance the understanding, prevention and management of both syndromes.

DR. FRED D. WEIDMAN, Philadelphia: The most useful information that emanated from our studies was the histologic. When interpreting disease changes, the pathologist attempts first to distinguish what kind of fundamental process it is that is producing the tissue changes in his materials, and he classifies them in the following manner:

1. Simple degenerative, meaning that there are not proliferative processes or inflammatory reaction (fatty degeneration, etc.)

2. The category of progressive tissue changes, just the opposite of the degenerative (hypertrophy, hyperplasia).

3. The inflammatory category, in which there is an inflammatory reaction. Others, such as cysts and tumors, are not relevant in the case of Ritter's disease.

The particular point that I wish to emphasize in Ritter's disease is the lack of inflammatory reaction. There is edema and congestion, but these are simple progressive changes. It requires cellular reaction and exudation of cells before one can state that the processes are in fact inflammatory. This was what Gilman and I found in our two necropsy cases, i. e., liquefaction degeneration and congestion. They were severe enough to produce utter disorganization of tissues at the junction of the epidermis and corium. They were of an order which might be produced by enzymes, bacterial or otherwise—"digestion" so to speak. Perhaps this is what Dr. Sulzberger had in mind when he used the term "microchemical" or "microbiologic" in his discussion.

As to differentiating between Ritter's and Leiner's diseases, I doubt that the problem will be solved until the cause is established. It is the old story—all of us are familiar with the differences in the characteristics, clinical and pathologic, of this or that disease entity (e. g., syphilis, lichen planus) depending upon the stage presented and we know it can be so radically different from stage to stage. It is permissible to discuss probabilities in the present situation but not to go farther.

DR. EARL W. NETHERTON, Cleveland: For personal reasons, I greatly appreciate having the opportunity to discuss Dr. Cole's paper but I do so reluctantly because, unfortunately, my concept of these diseases is based largely on knowledge obtained from the literature.

I have observed patients in which the diagnosis of Leiner's disease has been accepted by some observers. However, I cannot recall having seen a classic example of Ritter's disease. There is a noticeable paucity of articles pertaining to Ritter's and Leiner's diseases in the American literature. These dermatoses are rare indeed, and observers differ in their opinion regarding their relationship. Pediatricians and dermatologists on the staffs of children's and lying-in hospitals have a greater opportunity to become familiar with Ritter's and Leiner's diseases, which occur only in the newborn and slightly older infants.

Dr. Cole favors the opinion that Leiner's disease probably is a modified subacute form of Ritter's disease. He stated, however, that this is not the concept of European and some American authors.

These dermatoses are types of exfoliating dermatitis occurring in young infants and, as Hill (in Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1949, Vol. 4, Chap. 43) has stated, they must be differentiated from atopic erythroderma, which may complicate atopic infantile eczema. In the differentiation of these dermatoses, clinical features are more important than nonspecific histologic changes.

Although sporadic cases of Ritter's disease are observed, it is significant that epidemics of the disease occur and with concomitant development of bullous impetigo and other types of pyogenic eruptions. Furthermore, Nikolsky's sign is frequently observed in Ritter's disease.

The concept of some authors is that Leiner's disease usually starts with a marked seborrheic scaling of the scalp or as an intertrigo involving the groins and axillary folds. There is usually no exudation or Nikolsky sign and pruritus is not severe. Large, greasy scales develop on the forehead, face and extremities. Diarrhea is common, as Hill has stated, and is considered by some observers to be a necessary criterion for the diagnosis of Leiner's disease. Hill considers this dermatosis to be a severe seborrheic dermatitis of infancy. Unfortunately, little is known about the cause of seborrheic dermatitis.

In atopic erythroderma, which is seen in older infants, the incidence of family history of atopy is high. There is eosinophilia and intense pruritus. Seborrheic scaling of the scalp may occur. However, it is not a primary or important clinical feature. Skin tests to egg albumin are positive in atopic erythroderma but negative in Leiner's disease.

Dr. Cole's conclusion that Ritter's disease is probably caused by a staphylococcic infection in a debilitated infant with a lack of essential nutritive and immunologic factors is plausible and probable. However, there seems to be some justification for considering Leiner's disease as a different entity, and, as Hill has stated, it has been classified as a severe seborrheic dermatitis in infancy. Secondary impetiginous or pyogenic infection may complicate seborrheic dermatitis in adults, and, likewise, seborrheic dermatitis in infants. When this occurs, the clinical features of Ritter's disease are simulated.

The therapy recommended by Dr. Cole is excellent. Antibiotics are of special value in combatting staphylococcic and other bacterial infections. Vitamin B and supportive measures are particularly helpful, especially when there is a seborrheic component. Topical measures should be limited to bland protective remedies.

Dr. Harold N. Cole Jr., Cleveland: I would like to point out that recently in the pediatric literature, there have been a number of reports of cases which closely simulate Ritter's and Leiner's diseases. Actually, they are simply examples of dermatitis venenata and dermatitis medicamentosa resulting from the injudicious use of a combination of various baby oil preparations and boric acid ointment. I had occasion to see one of these cases recently, which on admission to the hospital was practically indistinguishable from the clinical picture of Leiner's disease.

REFERENCES

1. Ritter von Rittershain, G.: Central-Ztg. **2**:3, 1878.
2. Leiner, C.: Wien. med. Wchnschr. **57**:2459, 1907.
3. Leiner, C.: Arch. Dermat. u. Syph. **89**:163, 1908.
4. Sano, M. E.: J. Pediat. **23**:280, 1943.
5. Weidman, F. D., and Gilman, R. L.: Arch. Dermat. u. Syph. **167**:491, 1933.
6. Cailliau, F., and Fleury, J.: Bull. Soc. franç. dermat. et syph. **40**:884, 1933.
7. Binder, A.: Zentralbl. Gynäk. **63**:371, 1939.
8. Kendall, N., and Aegerter, E. E.: J. Pediat. **15**:733, 1939.
9. Guy, W. H., and Cohen, M.: Arch. Dermat. & Syph. **19**:425, 1929.
10. Neff, F.: Arch. Pediat. **51**:465, 1934.
11. Lee, H. F.; Wilson, R. B.; Brown, C. E., and Reed, T.: J. Pediat. **41**:159, 1952.
12. Widerman, A.: Am. J. Dis. Child. **70**:329, 1945.
13. Govan, C. D., Jr.; Cotton, A. L., and Rydeen, J. O.: U. S. Armed Forces M. J. **1**:682, 1950.
14. Schlesinger, H. A.: Arch. Pediat. **53**:175, 1936.
15. Wiener, A. S.: New York J. Med. **47**:1796, 1947.
16. Svejcar, J., and Homolka, J.: Ann. Pediat. **174**:175, 1950.

TREATMENT OF ACNE VULGARIS WITH ESTRONE

SAMUEL M. PECK, M.D.
EMIL G. KLARMANN, D.Sc.
AND
HERBERT J. SPOOR, Ph.D., M.D.
NEW YORK

ACNE VULGARIS is the commonest skin condition which a dermatologist is called upon to treat. It would be a conservative estimate to state that one of us (S. M. P.) has treated more than 3,000 cases during his dermatologic lifetime. With this experience in mind, it is justifiable to draw some general conclusions about therapy in this skin disease.

It is difficult to evaluate any therapeutic approach to acne vulgaris unless something is known of the course of the condition in any individual case, and unless the therapy in question is followed long enough to assay its results properly. We agree that the method of paired comparisons would be ideal, but obviously such a procedure is not practical in acne where a topical remedy is to be used at home by the patients for a period of months. A completely controlled study does not seem feasible.

The cases to be reported here were nearly all seen in private practice. A goodly number had been patients for a long time for their acne and some also for other skin conditions. We excluded from our material cases in which the course of acne, especially its fluctuations, could not be evaluated. Only in this way did we feel that the routine which we employed could be judged to some extent without paired comparisons. For this reason no patient was reported upon who had not been seen for at least six months prior to our study. A minimum observation period of three months was chosen arbitrarily to study the effects, especially on the recurrences. This accounts for the relatively small number of cases reported, although our work has been carried on for about two years, and approximately 200 cases have been treated.

Prior to World War II the standard treatment of one of us (S. M. P.) for acne called for the proper use of roentgen rays substantially along the lines of the plan suggested by George Miller MacKee. The results were satisfactory enough to warrant the conservative statement that with no internal treatment (other than diet) and with the use of topical remedies of the type of a mild white lotion (lotio alba) at least 75% of the cases could be considered practically cured in two years. While there were a fair number of acne pits still to be seen when the patient was considered cured, this was no more so than with the patients treated over the years when no x-ray treatment was employed.

Read before the Seventy-Fourth Annual Meeting of the American Dermatological Association, Inc., White Sulphur Springs, W. Va., April 15, 1954.

At this point, one of us (S. M. P.) feels compelled to state frankly why he has treated only 5% or less of his patients with roentgen rays in the last eight or nine years. Briefly, this was due less to the newer knowledge of the causes of acne or to the new chemotherapeutic agents introduced into therapy, than to the pressure of public opinion, both lay and that of the average practitioner, which has made it increasingly difficult if not impossible to employ this modality for the treatment of acne vulgaris. This statement holds true at least for the private practice in a city like New York.

The average case of acne with the exception of the so-called acne conglobata runs a self-limiting course of three to five years. The great majority of patients with acne do not seek medical help, especially that of a dermatologist; they respond well enough to relatively haphazard treatment, such as diet or topical remedies or both, to tolerate their skin condition. It is because of this that there exists today the widespread and popular appeal of the "over-the-counter" acne remedies which combine mild therapeutic action, like that of white lotion, with a camouflage to hide the blemishes until they disappear, either temporarily or permanently.

In a special group, as we have stated previously, are the severe acnes with the pustular elements predominating (acne conglobata included) and especially those of the recurrent type, in patients over 21 years of age, where there is a definite need of dermatologic advice.

As to the effect of diet upon acne vulgaris, it is the considered opinion of one of us (S. M. P.) that while diet influences exacerbations of acne, it alone has produced a clinical cure only in exceptional cases.

Vitamin A, whether given internally in large doses or applied externally, has proved disappointing as an important adjuvant in the treatment of acne; however, it seems to have some value in reducing blackhead formation in mild cases.

Perhaps it is well to outline here the current routine procedure of one of us (S. M. P.) (without the use of roentgen therapy) which has proved satisfactory enough, though not as effective as the use of roentgen rays, at least in some cases. The results obtained with this therapy have furthered the development of the hormone lotion which was used in treating the cases to be reported upon subsequently.

This treatment has been used for over 20 years and, conservatively speaking, about 2,000 cases have been exposed to it. It consists of (*a*) diet restriction, including avoidance of iodized salt, (*b*) the use at home of an antiseptic ointment (containing oxyquinoline sulfate 0.15; benzoyl peroxide 3.0; eucalyptol, thymol 0.3; petrolatum and wool fat [anhydrous lanolin] q. s. ad 30.0) or white lotion or sulfurated lime solution (Vleminckx's solution) and (*c*) treatment of the patient once or twice a week with various intensities of a cold quartz lamp followed by a 15 to 20 minute application of zinc oxide paste with salicylic acid (Lassar's peeling paste).

The mainstay of this treatment is induced desquamation and the local use of an antiseptic which has had proved value in well-established pyogenic processes of the pilosebaceous apparatus.

Such a course of treatment was about 10 to 12 weeks in duration. It was followed by a rest period of two to three months. The patients were instructed to continue local therapy at home. If there was a recurrence, another, perhaps

shorter, period of treatment with cold quartz and the zinc oxide paste was given again. Three to four such courses of treatment would be given in two years. In addition, when the zinc oxide paste was removed, blackheads would be expressed and, in some instances, lesions containing pus would be drained. Approximately 40 to 50% of the cases were controlled sufficiently by this method to be considered good results. It is taken for granted that in all cases, especially in those of acne conglobata, in which some of the most striking results were obtained, general supportive measures were also carried out at the same time when necessary.

A satisfactory result required more time than the routine use of roentgen rays, and in more than half the cases the therapy was not sufficient to bring about a clinical cure. The treatment seemed most eminently suited (even taking roentgen ray therapy into consideration) for young persons 13 to 16 years of age, and in acne conglobata, in which the results with roentgen rays are unsatisfactory, to say the least.

The introduction of the antibiotics in the recent past has highlighted the important role of the pyogenic organisms in the etiology of acne. While the use of various concentrations of Quinolor type ointment (containing a mixture of three derivatives of 8-hydroxyquinoline) was a good basis of proof for the role of pyogenic organisms, even more so was the striking though temporary effect of the ingestion of small doses of certain antibiotics such as oxytetracycline (Terramycin) (100 mg. three times a day) in bringing about a consistent disappearance of pustules and even of papules in some instances. It is in this group that autovaccine therapy has given the best results as far as permanent effects are concerned. It seems agreed that the need for prolonged administration of antibiotics plus their occasional collateral effects plus the recurrences when they were discontinued militate against the routine use of such a method of treament. Penicillin has been helpful only in acne conglobata and in the occasional furunculoid lesions which have been encountered.

In the use of autovaccine therapy (as against the preparation of stock vaccines and toxoids) one of us (S. M. P.) believes that the best results were obtained when he approached the problem of the role of the pyogenic organisms more as a sensitization phenomenon than as a pure infectious process.

The question of endocrine factors and the method of administration of estrogenic substance (whether internal or external) will be taken up in detail later. It is rather generally agreed that there is a highly significant endocrine factor in the etiology of acne vulgaris.*

EXPERIMENT I

A number of formula modifications were tested in an exploratory fashion before the final composition of the lotion was decided upon. Following is a summary of our observations upon certain ingredients entering into these modifications:

A. Hydroxyquinoline benzoate and orthophenylphenol seemed to be most efficacious as antibacterial agents when used in combination.

B. Coal tar did not add to the therapeutic value of the lotion; it had certain definite disadvantages, such as imparting an unsatisfactory color and showing an occasional tendency to increase blackheads.

* References 1 through 6.

C. Natural estrone seemed more satisfactory than synthetic diethylstilbesterol and dienestrol.

D. A concentration of estrone of 50,000 I. U. per ounce of vehicle seemed optimal.

E. Substantially more than 50,000 I. U. of estrone per ounce occasionally produced undesirable systemic effects.

Following is the final formula employed:

Final Formulation

Polyoxyethylene sorbitan monostearate	0.20%
Alkyl aryl polyethylene glycol	7.50
Wool fat, solubilized	2.00
"Proprionylated" lanolin	2.00
Oxyquinoline benzoate	0.25
Orthohydroxydiphenyl	0.50
Salicylic acid	0.625
Zinc sulfide	4.50
Zinc oxide	8.50
Sulfur, precipitated	5.00
Aluminum hydroxide	0.75
Lecithin, vegetable	0.20
Glycerin	3.95
Ethyl alcohol	11.60
Essential oils, mixed	0.25
Pigments, inorganic	0.05
Water	52.105
Estrone, natural q.s. to yield an estrogenic potency of 50,000 I. U. per ounce	

Results of Treatment.—The immediate effect in both groups (males and females) was good or excellent in 55 of 69 cases studied. There was also a positive effect upon the tendency to recurrence (suppression of activity of sebaceous glands) in both groups.

Considering the small number of males studied, the lotion seemed somewhat more efficacious in males than in females. There were not enough males, particularly in the younger age group, to determine the age relationship accurately. However, it is in the male group that we gained the impression that a tendency to recurrence was less pronounced when the therapy was stopped.

In the female group, too, there seemed to be a definite effect on the incidence of recurrence. Twenty-eight of the 53 cases appeared to be influenced favorably as far as recurrences are concerned. The age of the patients seemed to play a relatively minor role in the final response.

We would like to summarize here two cases which are typical examples of our experience with the hormone lotion.

Case 1.—S. C., a woman aged 20. This patient has been under treatment for approximately two years. When first seen, she presented a severe acne of several years' duration, consisting of papules and pustules with scarring. The eruption was especially marked in the bearded area. There was a tendency to hirsutism. Her menstrual periods were regular. She had had a variety of treatments consisting of diet, local antiseptics, zinc oxide paste with salicylic acid, cold quartz light and oxytetracycline internally. The treatments were quite unsatisfactory, with consistent recurrences.

In October, 1952, the patient was instructed to use a white lotion type of preparation. This was continued for about one month without much amelioration of her condition. Since the pustular element predominated she was given oxytetracycline, 400 mg. per day, with control of the pustular and papular part of her acne. There was prompt recurrence when the oxytetracycline was stopped. In December, 1952, the patient was put on a lotion which resembled our final formulation except that the estrogenic potency was only 25,000 I. U. per ounce. Apparently there was a very slight improvement in her condition. The periods remained regular during two months of medication. In April, 1953, the patient was put on the final formulation and has been doing well since then. In the last five months, there have been no recurrences. She has not used the lotion in more than three months.

Case 2.—This patient presents the other side of the picture. A woman, aged 38, had a marked papular-pustular acne which was more severe in the bearded area. Menstrual periods were irregular. She was treated with the lotion, but showed very little improvement over a period of five months. She was then given a series of roentgen ray treatments, with complete clearance of her acne.

Table 1.—*Blood Levels of the Estrogens*

Subject	Age	No. Days in Cycle	Time of Cycle †	No. Days Used Lotion	Estrogens at Start of Study,* γ	Estrogens at End of Study, γ	Difference in %
1. MW	28	30	LM	30	0.041	0.040	−2.4
2. ES	39	30	M	30	0.044	0.043	−2.3
3. ES	38	26	LM	26	0.039	0.038	−2.6
4. AC	30	30	EM	30	0.048	0.046	−4.2
5. EK	30	31	LM	31	0.031	0.031	0
6. GF	48	28	D	28	0.037	0.039	5.4
7. KK	60	..	A	30	0.028	0.030	7.1
8. EB	26	32	P	32	0.061	0.060	−1.6
9. PG	23	28	E	28	0.058	0.059	1.7
10. JS	29	27	M	27	0.043	0.041	−4.7
11. IB	31	male	....	28	0.005	0.005	0
12. HS	41	male	....	28	0.005	0.005	0

* Micrograms per 100 ml. whole blood (normals are 0.03-0.06 for nonpregnant women).
† Time of cycle refers to the time at which samples were taken. P, proestrum; E, estrum; D, diestrum; EM, early metestrum; A, amenorrhea; LM, late metestrum; M, metestrum.
Subject 6 is in her menopause and 7 has passed her menopause.

EXPERIMENT II

Influence of Daily Topical Application of Lotion on Blood Estrogen Levels and Vaginal Smears of Twelve Selected Human Subjects

Experimental Design.—Ten women ranging in age from 23 to 60 years and two men used as controls, aged 31 and 41, were observed over a period of one month during which they made one daily application of the final formulation to an area at least 8 in. (20.3 cm.) square of skin surface. Our objective was to learn whether or not this application induced any perceptible variation in the blood estrogen level, or in the length of the menstrual cycle, or in the monthly stage of vaginal cornification. Because of the normal cyclic estrogen changes and the cyclic variation in vaginal cornification, each woman used the lotion for one complete regular menstrual cycle. All women chosen had predetermined regular cycles except for one who was in her postmenstrual period. Each subject used the lotion for the number of days of her cycle, except for the postmenopausal subject (No. 7), who used it for 30 days. The men used the lotion for 28 days.

Blood estrogen and vaginal smear determinations were made at the beginning and end of the study period at the exact, theoretical daily time for most comparable

results (Tables 1 and 2). Variations between the initial and the final cyclic hormonal activity signs would have represented the effect of any percutaneously absorbed estrogen from the lotion under study.

The estrogen level of the whole blood of each subject was determined by the following methods: First, the quantity was approximated chemically by using the chromatographic method of Heusghem.[7] Then the exact concentration was determined by the guinea pig bioassay method of Littrell and Tom.[8] The method of Papanicolaou[9] was used to obtain, to stain, and to evaluate the vaginal smears.

Methodology:

A. The Heusghem[7] chromatographic method depends upon production of an estrogen-antimony-trichloride complex which is fluorescent in the shades of orange under ultraviolet light illumination. Chemically pure estrogen is used as control.

TABLE 2.—*Readings of the Papanicolaou Vaginal Smears*

Subject	Age	No. Days in Cycle *	No. Days Used Lotion	Smears at Start of Study †	Smears at End of Study †
1. MW	28	30	30	LM	LM
2. ES	29	30	30	M	M
3. ES	38	26	26	LM	LM
4. AU	30	30	30	EM	EM
5. EK	30	31	31	LM	LM
6. GF	48	28	28	D	D
7. KK	60	..	30	A	A
8. EB	26	32	32	P	P
9. PG	23	28	28	E	E
10. JS	29	27	27	M	M

* Subject 6 is in her menopause and 7 has passed her menopause.
† P, proestrum; E, estrum; A, amenorrhea; D, diestrum; EM, early metestrum; LM, late metestrum; M, metestrum.

B. The end point of the Littrell and Tom[8] bioassay is the amount of estrogen required to open the cervix of a virginal guinea pig. A time-dosage relationship holds.

C. Criteria used to evaluate the Papanicolaou[9] vaginal smears are as follows:

1. Staining reaction of the cells
2. Types and numbers of cells present
   - (*a*) Undifferentiated basal cells
   - (*b*) Differentiated basal cells
   - (*c*) Intermediate cells
   - (*d*) Superficial cells
3. Number of WBC, histiocytes, RBC

D. Subjects were policed in the use of the preparation, by demonstration, and through reminder calls.

Results.—The identification of subject, sex, age, number of days in cycle, stage identity of vaginal smear, and the amount of whole blood estrogen before and after completion of the prescribed use period are shown in Table 1.

Comparison of the Papanicolaou smears of the subjects before and after use of the lotion for a menstrual month is shown in Table 2.

The cycles were not altered in any way, and the vaginal smears showed no significant variation from one period to the next.

Interpretation.—No definite trend was noted in any of the blood estrogen levels of the subjects after daily use of the lotion. Six subjects' blood levels dropped 0.001 to 0.002 γ of estrogens per 100 ml. of whole blood, a decrease of approximately 4%, and three subjects' blood levels rose 0.001 to 0.002. The variation of 0.002 γ in the postmenopausal subject (KK) represented an increase of about 7% from the lower pretest level. One woman and the two men showed no variation. Since the method for quantitative determination in the blood is one of bioassay, the variations noted are in all probability within the limits of the method. By the same token, values below 0.005 γ as recorded for the men are near the lower limit of the method used.

There was no evidence of induced change in the menstrual cycle either through estrogenic increase prolongation of the cycle or through a change in the Papanicolaou vaginal smear.

Summary.—Application of the lotion to the glabrous skin of 12 subjects for periods of one month had no effect on their blood estrogen level, menstrual cycle, or vaginal cornification.

COMMENT

There is no doubt that in the pathogenesis of acne vulgaris we are dealing with a disease of the pilosebaceous system which is initiated originally by an endocrine imbalance, viz., between estrogens and androgens. This provides the basis on which other factors, perhaps of equal importance in some instances, may act as associated etiologic factors. Among such factors are foods, bacteria, climate, and even psychogenic moments. The bacterial factor is probably one of the more important. In mild cases, it can be said that acne is almost physiologic, at least as far as young males are concerned.

A great deal of experimental and clinical data have been gathered in recent years which are in support of the endocrine basis for the pathogenesis of acne vulgaris.†

The statistical studies of Bruno Bloch[1] in 1931 indicated rather conclusively that acne, especially that of the severe type, was more frequent among young males than among young females. Analysis of endocrine excretion has demonstrated in many cases that the ratio of the circulating estrogens to androgens is the critical factor. It seems to have been definitely established that the preponderance of the androgens supplies the precipitating stimulus, while the estrogens play the role of a counterbalance.

Hamilton[2] demonstrated the role of the androgens by showing that eunuchoid persons do not have acne vulgaris. He was able to produce acne in some castrated men, in ovariectomized women and even in boys before puberty, by administration of testosterone propionate. It is important to point out here that even in these experiments only a number of his subjects developed acne. Apparently, while the male sex hormone was important in affecting the activity of the sebaceous glands and in preparing the soil for acne, other associated factors were necessary for its development.

† References 1 through 6.

As Sulzberger and Witten [10] pointed out, the exacerbation of acne in relation to menses usually occurs a few days before the onset of the flow at the time when the androgen-estrogen ratio tends to be in favor of the former.

In recent years it has been observed occasionally that acne followed administration of corticotropin (ACTH) and cortisone. While this gives added support to the endocrine etiology of acne, it has been demonstrated further that factors other than endocrines may play an important role, since as with Hamilton's observations in eunuchoids, not all cases will develop acne under apparently the same dosage conditions. Here, too, there is evidence that administration of cortisone increases the quantity of circulating androgens.

Schwartz and Peck [11] have observed the routine precipitation of clinical and histologic acne lesions after external contact with chlorinated hydrocarbons, cutting oils, coal-tar pitch, etc. This occupational acne is produced without regard to the endocrine factor in the individual involved. Here, the causative mechanism depends upon a chemical finding its way into the openings of the sebaceous glands and stimulating the formation of keratin which leads primarily to comedo formation.[11] Bacteria are never found in such lesions, in contradistinction to acne vulgaris. While occupational acne is perhaps more easily elicited in those with an acne tendency (added irritant on a specially prepared soil), many of the acnegenic compounds seem to be capable of producing typical acne lesions at any site where there is an active pilosebaceous unit, in all age groups, and at sites where acne is not usually found. This seems to indicate that in some instances at least the endocrine factor is not essential.

In his experiments on the treatment of acne by subcutaneous implantation of estrogen pellets, MacKenna [12] found that:

1. Androgens stimulated the surface epithelium and the sebaceous glands, tending to produce hyperkeratosis and seborrhea.

2. Estrogens have a contrary action in that they diminish keratinization and the activity of the sebaceous glands.

One of the effects on the skin was referred to as follows:

> The growth of coarse hair on the face diminishes in vigor, so that daily shaving may be hardly necessary. The same effects may be obtained by the oral administration of stilbestrol, but in my experience unexpectedly large doses must be given for a considerable time. Similarly, local inunction with an ointment containing a synthetic estrogen in sufficient concentration has a remarkable effect on dandruff and on the surface hyperkeratosis; I have not employed it in acne to a sufficient extent to judge of its efficacy.

It is obvious, however, that relatively large doses of estrogens were necessary to produce such effects.

Even in Hamilton's cases, testosterone produced a more severe acne in castrates when there was a history of severe acne prior to castration.

In our introduction we discussed the role of bacteria as important etiologic agents in acne vulgaris. As far as we are concerned this seems to have adequate support both clinically and experimentally. The role of bacteria is quite obvious, considering the involution of acne lesions in many instances following administration of antibiotics such as oxytetracycline, and the improvement produced by topical application of wide spectrum bactericidal agents. Whether the bacteria play a role of sensitizing antigens or of direct infectious agents (as in furuncles) is not quite

clear. That bacteria are important but not entirely necessary to produce the picture of acne vulgaris is well evidenced by the experiments in the causation of occupational acne with chemical irritants [11] in which the absence of bacteria is a salient factor in the histologic picture.

It is known that carbohydrates, chocolate and, in some instances, iodine-containing foods (iodized salt) may also act as acne excitants.

Parenteral and oral administration of estrogen has proved of value in many cases of acne vulgaris.‡ To obtain a good result, fairly large doses have to be used in most instances. The local use of estrogens and its effect on acne vulgaris has been the subject of several reports. The results, while somewhat equivocal, are distinctly indicative.

Shapiro § treated 10 men and 15 women with a conjugated estrogenic (Premarin) cream containing 2.5 mg. of water soluble conjugated estrogens (equine) per gram of cream. This was applied once or twice daily for one to seven months. He reports excellent results in 15 patients.

Whitelaw [19] treated 72 males, aged 13 to 18, with an ointment containing 1.25 mg. of conjugated estrogens (substantially sodium estrone sulfate) per gram of vehicle. No other therapy was used. Within 14 days, definite improvement was noted in 90%. In the patients who were treated for six months or longer, 55% showed decided improvement, 21% slight improvement, and 24% failed to respond. In 23 females, 13 to 19 years of age, 21% responded satisfactorily and 12% showed moderate improvement. This author had no evidence of deleterious effects on clinical observation.

Sawicky, Danto, and Maddin [20] employed a cream resembling that of Shapiro's with respect to its estrogen content. The preparation was applied at bedtime to one side of the face, while the estrogen-free vehicle was applied as a control to the other side. There were 17 female and 9 male patients whose ages ranged from 13 to 29 years. The treatment was followed for a period of 2 to 16 weeks. Great improvement of the hormone-treated side was noted in three male patients with large cystic lesions. Patients with papular and pustular lesions showed moderate or no discernible improvement on the treated side.

A. J. Phillips [21] treated a total of 84 cases with Acnestrol. This lotion contains 1.75 mg. of diethylstilbestrol dilaurate per gram of base consisting of zinc oxide, talc, glycerine, water and isopropyl alcohol. Here, too, the hormone would seem responsible for any of the results observed since keratolytic and antiseptic agents appear to be absent. Phillips reported excellent to good improvement in 33 of 36 males, while only 3 females had what he considered excellent results.

It should be pointed out here that in the work referred to above, comparatively high potency estrogenic products were used as contrasted with the preparation upon which we are reporting. Sodium estrone sulfate 1.25 mg. per gram yields upon internal administration an estrogenic potency of 10,000 I. U. per gram, or about 300,000 I. U. per ounce.

Shapiro's cream contained 2.5 mg. of conjugated estrogenic substances per gram, substantially sodium estrone sulfate, corresponding to about 2 mg. of estrone per

‡ References 13 through 17.

§ References 18 and 19.

gram, or 600,000 I. U. of estrogen per ounce of cream, provided that it may be assumed that the estrogen is released completely from its ester bond for its topical action. The latter consideration applies also to Whitelaw's cream containing 0.625 mg. of sodium estrone sulfate per gram, or about 150,000 I. U. of estrogen per ounce of cream, as well as to the cream used by Sawicky, Danto, and Maddin containing 2.5 mg. of conjugated estrogenic substances per gram of vehicle as in the case of Shapiro's formula.

While the logical route of administration of hormones intended to affect sebaceous gland activity would be either the oral or the parenteral route, it should be kept in mind that too many physiologic disturbances are likely to result from the high dosages required for satisfactory results to advocate this form of therapy as a routine measure. Incidentally, in many instances, even such high doses did not bring about any improvement, to say nothing of any permanent results.

In deciding upon the final concentration of the estrogenic hormone in our formula, we were aware of the importance of using a hormone product which is known to have a definite effect on the epidermis. That such effects can be produced with estrone in doses even smaller than we have included in our lotion has been well documented by many observers. This point is being emphasized because we are not aware of any published or other authoritative information concerning the skin's capacity to utilize sodium estrone sulfate. If, as seems probable in the light of the several clinical studies referred to above, the skin can utilize this substance, the question arises immediately as to whether any hydrolysis with formation of free estrone must precede its dermal integration, and, if so, to what extent. In connection with the systemic action following upon the oral administration of sodium estrone sulfate, there is reason to believe that its hydrolysis takes place in the liver whence estrone is released to perform its physiological function. However, we do not know whether the skin is capable of acting in a similar manner, or indeed whether it is called upon for such action.

To affect the various types of bacteria which are commonly isolated from lesions of acne vulgaris such as Staphylococcus aureus, hemolytic Staph. aureus, Staph. citreus, Staph. albus, and Streptococcus, a wide spectrum antiseptic agency should be used. This we believe to have achieved by the combination of oxyquinoline benzoate and orthophenylphenol. Tying their action to that of sulfur, we would have agents useful for quick amelioration of the acne lesions. To decrease the incidence of recurrences, we attempted to change the "acne soil" by utilizing estrone for its effect on the activity of the sebaceous glands. As to the final concentration of the hormone, we were guided by the results of our preliminary experiments which indicated that the minimum dosage for consistent clinical effects was in the neighborhood of 50,000 I. U. per ounce. As stated before, we could not demonstrate any systemic effects from this hormone concentration. We also had the impression that the natural estrone had a better local action than the synthetic stilbestrol.

With one preliminary preparation containing 150,000 I. U. of estrone per ounce of vehicle, we noticed, in a few cases, indications of disturbances such as effects on the menstrual periods.

Although acne has its original start with a hormonal imbalance, we agree with Sulzberger and Witten [19] that modern hormone therapy alone, be it parenteral, oral,

or even topical, has not proved of more than partial value in the management of this disease. Of the three routes of administration, the topical route, correctly handled, seems to offer the greatest promise of success.

We believe that the true cure of acne is still to be attained. The preparation with which we have been working seems to represent a distinct step forward, combining as it does hormonal, antibacterial, keratolytic, and astringent qualities, all of them relevant to the control of acne symptoms. Of course, medication with a preparation of the type under discussion cannot be expected to provide the finality of results which can be obtained, under favorable circumstances, with adequate doses of roentgen rays. In most instances, prolonged application of any medication is necessary whenever the topical control of symptoms does not run parallel with the systemic control of their inciting cause. For the same reason, recurrences are likely to appear upon discontinuance of such medication therapy, since the inciting factors presumably are still operative at full intensity. It should be pointed out, however, that in a number of our cases a return to the previous level of acne activity occurred only several months after discontinuance of lotion therapy; in some cases, apparently no such recurrence took place at all.

The sustained good effects were noted mostly in those patients who used the preparation longer than four months and who followed instructions to continue its use for at least two or three times a week even when there were practically no lesions to be seen. We have no way of knowing how many of our patients would have had permanently good effects upon discontinuance of the therapy.

Our findings compare with those of other investigators with respect to demonstrating a better effect in males than in females.

SUMMARY AND CONCLUSIONS

Laboratory and clinical data are presented on the efficacy of a lotion which combines keratolytic, antibacterial, and estrogenic principles for the treatment of acne vulgaris.

By way of immediate effects, good to excellent results have been obtained in 55 of 69 cases studied.

Apparently, the topical application of estrogenic hormones (50,000 I. U. per ounce) plays a significant role in controlling the recurrences, presumably by decreasing the activity of sebaceous glands; the remaining components of the lotion appear to influence the other manifestations of acne lesions already present.

There was no evidence of any systemic effect from the daily application of 50,000 I. U. of estrone per ounce of this lotion when used for a period of one month.

The lotion seemed to have a somewhat better effect on males than on females.

Mr. P. H. Cox helped with the formulations.

ABSTRACT OF DISCUSSION

Dr. Richard L. Sutton Jr., Kansas City, Mo.: No two of us, I suppose, interpret acne the same way or treat it the same way. Dr. Peck and his collaborators require little apology for their difficulty in setting up controls for their study. Looking upon acne, as I do, as a cutaneous manifestation of systemic disorder of endocrine and metabolic functions, I should consider the results of comparing the two sides of the face, treated differently, as possessing the same kind of significance as the results of treating differently the two hands of a patient with pellagra or

the two elbows of one with eruptive xanthoma. I suppose an especially suitable group of patients for study would be the adolescents of a boarding school, whose ways of life and diets and ages would be fairly uniform, though unavoidably not identical.

Dr. Peck and collaborators have given emphasis different from that which I (Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949, p. 405; Sutton, R. L. Jr.: Treatment of Acne Vulgaris, Experimental Use of Cortisone, *J. Missouri M. A.* **49**:471-475 [June] 1952) should give to the significance of pyogenic infection in etiology. I consider parasitism purely secondary when it occurs. However that may be, I shall not object vigorously to inclusion, among the 18 ingredients of their topical medicament, of 4 ingredients to combat parasitism, if one counts sulfur and salicylic acid as such. That leaves 13 ingredients for conveying medication to the recipient, plus the 1 ingredient primarily intended to be studied—the estrogenic one. If I were studying it, my formula would probably include 3 other things, rather than 17.

I have learned to agree with Dr. Goeckermann (Goeckermann, W. H.: Hormonal Therapy of Acne Vulgaris in the Female, ARCH. DERMAT. & SYPH. **61**:237-241 [June] 1950; Goeckermann, W. H., and Wilhelm, L. F. X.: A. M. A. ARCH. DERMAT. & SYPH. **66**:402-403 [Sept.] 1952) that estrogenic substances are often beneficial in acne. Decisions as to which patient needs estrogen and how much, are as yet somewhat difficult for me to make. I would generalize to this extent: Estrogen will probably help a girl whose periods are of more than five days duration, who suffers cramps during the first day or two of the period, whose breasts are sore a day or two before the flow, and whose acne manifests undeniable premenstrual flares. When menses are normal and when these four clinical indications of estrogen deficiency are absent, the administration of estrogen has, in my experience, regularly but only transiently produced undesirable effects.

Parenthetically, excessive estrogen administration may stop ovulation so that a girl misses a period or two, or perhaps an ovulatory bleeding may occur. I don't take too seriously the missing of a period. I don't feel that a person would be harmed by a temporary overdose. If you want to pour on estrogen, wait until the girl ovulates, and then give it to her in any dose you want, until the next menstrual flow has ended.

The right dose of estrogen is likely to be, I find, from 0.3 to 0.625 mg. of conjugated estrogenic substances (Premarin) a day by mouth, roughly 3,000 to 6,000 I. U., and larger doses have seldom been correct. Lately, I have been giving estrogenic substances to almost all acneic males, holding down the dose to one which does not produce sore nipples or enlargement of the breasts.

Limiting discourse to the effects Dr. Peck and co-workers obtained with estrogenic substances topically applied, in a concentration of 50,000 I. U. per ounce, we may consider the effect of giving a dose of estrogen percutaneously, which is not defined by them as to quantity beyond saying that it did no demonstrable harm, for they did not state how many days it took to use an ounce of the ointment or give other measures of the dose on which one could arrive at the dose arithmetically.

To obtain some idea of what dose was absorbed by their patients, many of whom were helped and none of whom was harmed, let's think this way: If the average daily application amounted to 2 gm., the topical dose was then, roughly, 50,000 divided by 15, which equals 3,000 I. U., in round figures, equivalent to 3 mg. of conjugated estrogenic substances daily. The results of Dr. Peck and colleagues then, from putting something like 3,000 I. U. per day onto the skin, resembled my results from putting some 3,000 I. U. per day into the stomach. One may therefore assume that almost all of their topically applied estrogenic substance was absorbed—an interesting although not a reliable inference.

When I treat acne without investigative purposes, noting that investigation was the purpose of Dr. Peck and his associates, I try diligently to establish endocrine balance and to give the patients individually correct doses of thyroid and/or estrogenic hormone. I (Sutton, R. L., Jr.: Acne Vulgaris a Pustular Lipoidosis, *South. M. J.* **34**:1071-1082 [Oct.] 1941) have long ago described the practical clinical technique of establishing the correct dose of thyroid, which is the largest dose causing no detectable indication of overdosage. Some acne patinets do not need any thyroid, but most of them do. Fears expressed by timid souls concerning the clinical determination of correct thyroid dosage, as I determine it, are due only to their inexperience.

Dr. Peck and co-workers have added confirmation, I should say, to the views that estrogens are often helpful to patients with acne; that modest doses are seldom harmful, and that the hormone can be given percutaneously with effectiveness. I hesitate to concur with the belief that the topical method of giving estrogen offers the greatest promise of success, for I think correct dosage would be as easy to establish with pills as with ointments.

Dr. Frank L. Eichenlaub, Washington, D. C.: I do not particularly wish to discuss the hormonal treatment of acne, either local or internal, because my own results with both have been very disappointing, but I should like to make one remark about the authors' fear of using x-ray in the treatment of acne.

Personally, I think that, properly used x-ray treatment is going to be much less harmful to patients in the end than the prolonged use of antibiotics or the prolonged use of estrogens, etc. At least, we know that the damage to the skin will be from the x-ray that we use—the little damage we will get if it is properly used. Up to now, we don't know what the end-effects of some of the other treatment may be.

Dr. Henry A. Brunsting, Toledo: The paper presented by Dr. Peck and his colleagues has a great deal of merit. They are fully cognizant of the danger of drawing conclusions from the study of such a small series of patients. They are aware of the difficulty and have anticipated criticism of lack of proper controls. One might question the incorporation of keratolytic and bacteriostatic agents along with a hormone in their therapeutic mixture.

In Experiment II, the authors demonstrate that there was no systemic absorption following topical application of the hormone lotion in 12 subjects, 9 being females with normal menstrual cycles, 1 a female in the postmenopausal period, and 2 being males. One might ask what would occur in a larger series of subjects with both regular and irregular menstrual cycles? Also the effect when the hormone lotion was applied to different sites of the skin surface, broken and unbroken?

The authors state they considered a concentration of estrone of 50,000 I. U. per ounce of vehicle optimal, and that substantially more than 50,000 I. U. produced undesirable systemic effects, the nature of which were not defined.

It is interesting to note that in the last eight or nine years, the authors have used roentgen therapy in less than 5 out of every 100 patients with acne. This opinion may be shared by many who used roentgen therapy 20 or more years ago, and no doubt may likewise apply to the indiscriminate use of the corticosteroids and other hormonal agents that may haunt us in the days to come.

The judicious use of roentgen rays in selected cases of acne is still one of the best single therapeutic agents we have at our command.

The etiologic factors and morphologic characteristics of acne are multiple and complex. In appraising a therapeutic agent, one should define the type of acne with which he is dealing. Patients with acne may be divided roughly into the following groups, which may again be subdivided.

1. Acne, adolescent, mild type: sex incidence probably equal; seborrhea and comedone formation present, may be pronounced; can be considered a physiologic process, appearing at time of secondary sex characteristics; no clinical evidence of any real endocrine abnormality present; controlled by diet and mild keratolytic and bacteriostatic agents; roentgen and hormonal therapy not indicated.

2. Acne, papulopustular, cystic, moderate to severe, including acne conglobata and so-called tropical acne: incidence greater in male sex; comedone and double comedone formation pronounced; cysts and secondary infection characteristic; hormonal therapy usually without benefit; antibiotic and roentgen therapy of value.

3. Acne, adult, premenstrual: implies occurrence in female sex, although not unusual in males; age group 25 to 50 years; lesions cystic, usually not infected; distribution frequently chin and forehead, between the eyebrows; comedone formation absent; emotional factors frequent; treatment difficult; diet, topical applications and roentgen therapy usually ineffective; in this group, endocrine therapy may prove to be beneficial.

4. Acneform eruptions—such as chloracne, and eruptions due to bromides, iodides, corticosteroids, masculinizing tumors, etc.: not acne in the true sense.

The statement has been made many times, that one of the etiologic factors in the production of acne is the imbalance in the ratio between the circulating androgens and estrogens, with probably an excess of androgen. We speak of this rather glibly, yet do not understand the exact mechanism and all the implications. There may be wide variation in the ranges even in the apparently normal person without acne. Therapeutically our attempts in restoring this equilibrium have been equivocal.

Many contradictory reports of the effectiveness of various hormonal agents have appeared in the literature. It is noteworthy, I believe, that the majority of reports on this subject deal either exclusively or excessively with the female sex, and that the poor male, without a menstrual cycle, has been neglected.

Interest in the hormone treatment of acne has extended beyond the medical profession. Recently, the mothers of a number of my patients with acne, called to my attention an item which appeared in the March, 1954, issue of *Good Housekeeping Magazine*, which stated, "Solutions of estrogen were used to treat 38 women with acne. Significant improvement was reported in all 38 cases."

Since the column in this magazine entitled, "Keep up with Medicine" was unsigned, I took the trouble to write the Editor of *Good Housekeeping Magazine* requesting information concerning the source of this material. A few days later, I received a very courteous reply from Dr. Morris Fishbein stating that he conducted this column and that the information was obtained from the July, 1953, issue of the *Journal of Clinical Endocrinology and Metabolism*.

On reviewing the original article, I learned that the authors stated, "Of the 38 patients treated, 29 required both local and systemic therapy. Nine patients responded adequately to local therapy alone."

In the unsigned article in *Good Housekeeping Magazine*, it was stated, "If you want to know more about any item, consult your physician." And that, gentlemen, is probably one of the reasons why we are here today discussing this subject.

Dr. Lawrence G. Beinhauer, Pittsburgh: I am reporting my clinical observations of 75 patients, in the age group of 16 to 32 years, 40 females and 35 males. The period of observation was four months to one year. The patients had the acne for two to four years.

The estrogenic substance used was 100,000 units per ounce of diethylstilbestrol, in a calamine lotion.

To combat secondary infection, we added cinnabar 1% to the lotion.

The untoward reactions encountered were as follows: Four males complained of slight mastitis of the breasts, which disappeared within six weeks after the cessation of the drug; four females complained of irregularity of periods varying from one week early to one to three weeks late; one female had no period for a period of six months. These reactions were manifested after four to six weeks of medication.

The end-results were no better than those in which topical applications with sulfur and resorcinol were used. In our experience, the results were rather disappointing.

Dr. Frederic T. Becker, Duluth, Minn.: I, too, have been looking for a better preparation in the local treatment for acne. An external application which could reduce the activity of the sebaceous glands and inhibit the bacterial growth without the untoward reactions encountered in the oral use of estrogens and antibiotics would be ideal. I have used a lotion containing 1.0 mg. of sodium estrone sulfate per cubic centimeter. Roughly, this is less than one-half the dosage that Dr. Peck utilized.

Twenty-five student nurses were selected, as they were under the same environmental conditions, and their ages ranged from 17 to 20 years. Two lotions which were identical in appearance were used, except that one contained the conjugated estrogens. Their content was not known until after the tabulation of the results, as they were labeled "A" and "B." Of the 25 nurses treated, 22 were followed for a minimum of six months; 11 were treated with lotion A, and 11 with lotion B. At the end of six months, the results were evaluated. I could see no difference between the placebo lotion and the one containing the hormone.

DR. SAMUEL M. PECK: I did not express any fears of x-rays. Perhaps I slurred over that portion. In the paper, you will find that I was very careful to state that I think, taking cases as they come, x-ray is still the best single approach we have to the treatment of acne. I was careful to state that I was very happy with the technique and dosage forms originally suggested by Dr. MacKee. I said it was the pressure of public opinion which forced me to use less and less x-ray treatment, not my own desire. I was perfectly happy with the treatment, and I think it is quite safe in the hands of those who know how to use x-rays.

As far as absorption is concerned, we have carried out other experiments, using a much better base for absorption than a lotion. We go along with Dr. Adlesberg that at best, no more than 20% of the hormone is absorbed after topical application. I believe that our previous experiments with absorption of tripelennamine (Pyribenzamine) through the skin certainly point out the danger of the marked increase of absorption through broken skin, so I agree that you may get more absorption, the more the skin is damaged.

As far as systemic effects are concerned, we tried not to formulate the lotion in such a way that we would get the minimum possibility of systemic effects. Mind you, we carried out our experiments over a limited area of skin, for a period of one month. Perhaps, if we had carried them out for many months, with our dosage forms, we might have seen evidence of absorption.

We agree with the discusser who said he saw no effects from 25,000 units. The only effect that we possibly attributed to the hormone was a lessening of the recurrences. Mind you, I stress that point. We believe that with less than 50,000 units of estrone per ounce, we were unable to get appreciably difference in results. With more than that, we got more satisfactory results. But we also had systemic effects, and that is why we dropped down to the dosage which we finally used.

REFERENCES

1. Bloch, B.: Metabolism, Endocrine Glands and Skin Disease, with Special Reference to Acne Vulgaris and Xanthomata, Brit. J. Dermat. **43**:61, 1931.

2. Hamilton, J. B.: Male Hormone Substance: A Prime Factor in Acne, J. Clin. Endocrinol. **1**:570, 1941.

3. Wile, U. J.; Snow, J. S., and Bradbury, J. T.: Studies of Sex Hormones in Acne: II. Urinary Excretion of Androgenic and Estrogenic Substances, Arch. Dermat. & Syph. **39**:195, 1939.

4. Goldzieher, M. A.: The Endocrine Pathogenesis and Treatment of Acne Vulgaris, M. Rec. 160, 1947.

5. Sulzberger, M. B., and Baer, R. L.: Acne Vulgaris and Its Management, in The 1949 Year Book of Dermatology, Chicago, The Year Book Publishers, Inc., 1950.

6. Cornbleet, T., and Barnes, B.: Hormones and Acne Vulgaris, Arch. Dermat. & Syph. **40**:249, 1939.

7. Heusghem, C.: Paper Partition Chromatography of Natural Oestrogens, Nature, London **171**:42, 1953.

8. Littrell, J. L., and Tom, J. Y. S.: Fluctuations in Estrogen Level Throughout the Menstrual Cycle of One Woman, Endocrinology **40**:292, 1947.

9. Papanicolaou, G. N., and Traub, H. F.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, The Commonwealth Fund, 1943.

10. Sulzberger, M. B., and Witten, V. H.: Hormones and Acne Vulgaris, The Medical Clinics of North America, Nationwide Number, Philadelphia, W. B. Saunders Company, 1951, p. 373.

11. Schwartz, F., and Peck, S. M.: Occupational Acne, New York J. Med. **43**:1711, 1943.

12. MacKenna, R. M. B.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1948.

13. Way, S. C., and Andrews, G. C.: Hormones and Acne: Clinical Evaluation of Hormonal Therapy in Adolescent Girls with Acne, Arch. Dermat. & Syph. **61**:575, 1950.

14. Bernbery, C. H., and Rein, C. R.: Treatment of Acne Vulgaris: Preliminary Study on Value of Pregnant Mare's Serum, J. Clin. Endocrinol. **4**:65, 1944.

15. Goeckerman, W. H.: Hormonal Therapy of Acne Vulgaris in the Female, Arch. Dermat. & Syph. **61**:237, 1950.

16. Baird, K. A.: Effective Approach in Treatment of Acne, J. Invest. Dermat. **12**:317, 1949.

17. Miescher, G., and Stark, O.: Problem of Treatment of Acne, Dermatologica, **101**:275, 1950.

18. Shapiro, I.: Estrogenic Treatment of Acne Vulgaris, Preliminary Report, J. M. Soc. New Jersey **46**:128, 1949.

19. Shapiro, I.: Estrogens by Local Application in Treatment of Acne Vulgaris, A. M. A. Arch. Dermat. & Syph. **63**:224, 1951.

20. Whitelaw, M. J.: Treatment of Adolescent Acne with Topical Application of Estrogen, J. Clin. Endocrinol. **11**:487, 1951.

21. Sawicky, H. H.: Danto, J. L., and Maddin, W. S.: Clinical Evaluation of Topically Applied Estrogen Cream in Acne Vulgaris, A. M. A. Arch. Dermat. & Syph. **68**:17, 1953.

22. Phillips, A. J.: Topical Estrogens in Acne Vulgaris, New York J. Med. **51**:1313, 1951.

GRANULOMA ANNULARE

Response to Massive Dose Therapy of Vitamin E Combined with Pantothenic Acid Derivatives

ASHTON L. WELSH, M.D.
CINCINNATI

PRELIMINARY [1] and supplemental [2] reports have been made on the response to, and rationalization for, the use of massive dose therapy of vitamin E combined with pantothenic acid derivatives in certain phases of lupus erythematosus — a disease in the cutaneous lesions of which "the common denominator is the connective tissue." [3] The present study of results obtained in the treatment of granuloma annulare reports favorable response to similar massive dose therapy in another disease entity characterized by collagenous degeneration.

Materials used in this study * were essentially those used in the treatment of certain phases of lupus erythematosus.[2] Rationalization for study of response to these agents in the treatment of granuloma annulare is as follows:

1. The etiology of granuloma annulare is not known.† Opinion remains divided regarding the concept of a polyetiologic syndrome incriminating tuberculosis ‡ and rheumatoid arthritis,§ on the basis of histologic findings,‖ toxic origin, and vascular changes,¶ but causative factors remain unproved.#

2. Early manifestations of granuloma annulare appear in alterations of the connective tissue.* Vasculitis, endarteritis, and periarteritis are constantly present,[29] and the more or less inflammatory reaction surrounding the blood vessels suggests that the beginning necrosis may be conditioned by some alteration of the vessels.[30]

3. Experience with use of the tocopherols as internal therapeutic agents indicates that vitamin E exerts some profound influence on collagenous degenerations.† Burgess ‡ reported favorable results, in the majority of his observations,

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* Pantothenic Acid Derivatives were obtained as Panthenol from Hoffmann-LaRoche, Inc., and as Calcium Pantothenate Dextrorotatory from Lederle Laboratories Division, American Cyanamid Company; Merck & Company, Inc., and Chas. Pfizer & Company, Inc. Vitamin E was obtained as Ephynal Acetate from Hoffmann-LaRoche, Inc., as Natopherol Acetate from Abbott Laboratories, and Distillation Products Industries, Division of Eastman Kodak Company and as Aquasol E from U. S. Vitamin Corporation.

† References 4, 5, 6, 7, 8 and 9.

‡ References 10 through 14.

§ References 15, 16, and 17.

‖ References 18, 19, and 20.

¶ References 21 through 24.

References 25, 26 and 27.

* References 10 through 24 and 28.

† References 1, 2, 31 and 32.

‡ Reference 31 and 32.

in the treatment of patients who had granuloma annulare, lichen sclerosus et atrophicus, scleroderma, morphea, and long-standing granulomatous leg ulcers, his results paralleling those of MacKenna.[33] It was emphasized that therapy should not be discontinued with apparent cure, but must be prolonged thereafter for maintenance. Cochrane[34] reported a series of patients with granuloma annulare who responded to similar therapy. Hagerman[35] reiterated that vitamin E therapy must be prolonged after response is obtained.

4. The complimentary role of pantothenate has been described.§ Recent work indicates that the effectiveness of certain materials, apparently acting through the pituitary-adrenal system, are enhanced when administered with calcium pantothenate.‖

It was this investigator's postulation[2] that the "metabolic products of vitamin E, such as quinones, may serve as 'building blocks' to aid in the formation of cortisone-like materials, which are presumed to be excreted by the adrenals. Calcium pantothenate may be an additional biological catalyst, along with the adrenocorticotropic hormone to help aid in the formation of new cortisone-like materials." Confirmatory evidence of this postulation exists.[36] The tentative assumption is that by making an ample supply of calcium pantothenate available, the adrenal cortex, when properly stimulated, may then be able to meet the emergency requirements for rapid synthesis and an unusually large output.[36]

CLINICAL DATA

Nine patients with granuloma annulare—five females and four males—constitute this series of patients who received massive dose therapy of vitamin E combined with pantothenic acid derivatives. All patients presented dermatoses which were typical, clinically, of the disease. Diagnosis was confirmed in seven patients by biopsy. Sex, incidence, and distribution of lesions are comparable to the experience of Ellis and Kirby-Smith,[38] and to series data, as reported by them, from the literature. Unusual location and distribution of lesions are comparable to cases reported by others.¶ Only one patient had had previous therapy (consisting of gold, bismuth, arsenic and x-ray), without favorable response.

DOSAGE SCHEDULE

Daily dosage of pantothenic acid derivatives varied from 5 gm. in children to 10 gm. in adults. Daily dosage of vitamin E varied from 0.3 gm. in children to 1.25 gm. in adults.

No complications and no reactions, attributable to therapy, were evidenced. (Patients recently started on treatment, and not included in this report, are receiving orally, daily, in addition to pantothenic acid derivatives and vitamin E, 1.0 gm. of vitamin C and 100 γ of vitamin B_{12}. Rationalization for such supplemental therapy is based on acquisition of knowledge since this study was undertaken.)#

§ References 1 and 2.

‖ References 36 and 37.

¶ References 39 through 41.

References 39 through 50.

LABORATORY DATA*

Urinary excretion levels of pantothenic acid in these patients before institution of therapy averaged 25.6 γ per milliliter. An average level of 2.69 γ per milliliter was obtained in normal persons used as controls.

Blood plasma levels of pantothenic acid in these patients with granuloma annulare averaged 16 γ per 100 ml. An average level of 27 γ per 100 ml. was obtained in normal persons.

Average blood levels of vitamin E in these patients was 1.07 mg. per 100 ml. serum. An average level 2.37 mg. per 100 ml. was obtained in normal persons used as controls.

The high pantothenic acid excretion level and low vitamin E blood level, before institution of therapy, parallel closely the findings I have reported in patients with lupus erythematosus.[2] The relatively low blood plasma level of pantothenic acid is similar to recent unpublished findings in patients with lupus erythematosus.

RESPONSE TO THERAPY

In eight patients the condition cleared completely. In the very young patients and in patients whose lesions were of short duration, the condition cleared more quickly than in older patients and in patients whose lesions were of long standing.

One patient (No. 9) improved gradually during several months of therapy and then disappeared from observation. He reappeared in a hospital with a systemic and local fungous infection (Rhizopus), manifesting lesions of the latter in the original plaque of granuloma annulare. The satellite annular and papular lesions of granuloma annulare had completely disappeared.

In four patients (No. 1, No. 3, No. 6, and No. 7), treatment was discontinued almost immediately or very shortly after apparent clearing of the skin lesions. Patient No. 1 relapsed after one month. He developed two lesions in the sites of the old lesions. These lesions cleared in a month after resumption of treatment. Patient No. 3 relapsed after a month. She developed two new lesions. The lesions promptly cleared again in a month after treatment was resumed. Patient No. 6 developed some recurrence in edge of three old lesions on dorsa of hands after being off treatment for two months. These lesions disappeared after two more months of treatment. Patient No. 7 relapsed two months after treatment was discontinued. She developed two lesions in the sites of the old lesions. The skin is now nearly clear three months after resumption of treatment. In these four patients, the interval required for clearing of the recurrent lesions, after resumption of treatment, varied directly with the time elapsed between recurrence and resumption of treatment.

In the remaining patients (excepting No. 9), the treatment was not discontinued but gradually reduced to maintenance dosage of 0.5 gm. calcium pantothenate and 100 mg. of vitamin E daily. In two of these, No. 5 and No. 2, after slow withdrawal and maintenance of the above level for several months, treatment has now been completely discontinued for four months and five months, respectively, without recurrence.

* Laboratory studies were made by Hill Top Research Institute, Cincinnati.

Response to Therapy

Patient	Age (Yr.)	Sex	Duration of Disease (Mo.)	Biopsy	Type of Lesions	Distribution	Daily Dosage Schedule: Pantothenic Acid Derivatives (Gm.)	Daily Dosage Schedule: Vitamin E (Gm.)	Results
1. R. L.	9	M	1	Positive	Two quarter-sized annular lesions with central clearing; bluish-red papules at periphery	Dorsum right wrist; right buttock	5.0	0.5	Cleared in 5 mo.
2. J. P.	29	F	3	—	Three edematous, erythematous, annular lesions; borders elevated	Left cheek	10.0	1.0	Cleared in 2½ mo.
3. C. F. McQ.	30	F	36	Positive (2 specimens)	Plaques, 3 to 5 cm. in diameter—gyrate lesions with active borders and central clearing; annular lesions, 1 to 3 cm. in diameter; satellite papules	Generalized, accentuated on extensor surfaces of extremities. Scalp, palms and soles clear	10.0	1.0	Cleared in 14 mo.
4. L. F.	38	F	6	Positive	Annular, silver-dollar-sized lesions; central clearing; borders elevated; reddish-blue papules	Right side forehead	10.0	1.0	Cleared in 23 mo.
5. M. G.	1.5	M	1.5	Positive	Umbilicated papules; annular lesions, 1-2 cm. in diameter; firm, elevated borders	Generalized, accentuated on buttocks and extensor surfaces of extremities	3.0	0.3	Cleared in 1 mo.
6. L. C. L.	70	M	24	Positive	Gyrate and annular plaques, 4 to 10 cm. in diameter; central clearing; elevated, bluish-red, firm borders	Back of neck; dorsa of hands and wrists	7.5	1.25	Cleared in 17 mo.
7. J. A.	0.8	F	4	—	Annular lesions, 1 to 2 cm. in diameter; central clearing; borders elevated, surrounded by reddish areola	Buttocks and extensor surfaces of extremities	6.0	0.6	Cleared in 5 mo.
8. B. K.	37	F	12	Positive	1 to 3 cm. in diameter, annular lesions; red to purple, elevated borders; some satellite papules; central clearing	Extensor surfaces, upper half of each forearm	7.0	1.0	Cleared in 1½ mo.
9. L. O.	5	M	24	Positive	Plaque, 7 cm. in diameter; annular and indurated papular lesions, 1 to 2 cm. in diameter; center of plaque, cicatricial	Right chest, extending into right axilla	5.0	0.5	Disappeared from observation after 7 mo.; when last seen, much improved

COMMENT

The clearing of the lesions of granuloma annulare in eight patients and improvement in the ninth patient treated with massive dosage of vitamin E combined with pantothenic acid derivatives suggests that this is an effective method of treatment. The fact that relapse occurred in four patients when treatment was discontinued soon after apparent clearing, plus the fact that the lesions rapidly cleared again when treatment was resumed, support the thesis that the clearing was due to the therapeutic agents employed. The fact that there was no relapse in the patients in whom the dosages of the vitamin E and pantothenic acid derivatives were reduced slowly to the above recorded maintenance level further supports the thesis that these agents are effective therapeutically in patients who have granuloma annulare.

CONCLUSIONS

Massive dose therapy, consisting of vitamin E combined with pantothenic acid derivatives, constitutes a safe and effective approach to treatment of patients who have granuloma annulare.

ABSTRACT OF DISCUSSION

DR. JOHN GODWIN DOWNING, Boston: Dr. Welsh has presented a new therapy for a protracted cutaneous disturbance. A safe efficient method of therapy is always welcome. In view of his selection of diseases for therapy with vitamin E combined with pantothenic acid derivatives, I thought a brief history of granuloma annulare might be of interest.

In 1893, Radcliffe-Crocker (Lupus Erythematosus as an Imitator of Various Forms of Dermatitis, *J. Cut. & Gen.-Urin. Dis.* **12**:1-9 [Jan.] 1894) read before this Society at the annual meeting in Milwaukee a paper on lupus erythematosus as an imitator. He described a young man 20 years old with annular lesions on the face and hands. In this report, he mentioned a patient of Colcott Fox whom he had seen in consultation. In 1895, the latter (Society Intelligence, *Brit. J. Dermat.* **7**:91-92 [March] 1895) at a meeting of the British Dermatological Society of London showed a girl 11 years old with a ringed eruption on the fingers. According to MacLeod (Diseases of the Skin, New York, Paul Hoeber, 1921, pp. 673-677), he was the first to recognize it as a separate entity. In 1902, Radcliffe-Crocker (Granuloma Annulare, *Brit. J. Dermat.* **14**:1-9 [Jan.] 1902) reported several cases in the *British Journal of Dermatology* and labeled this entity granuloma annulare. Since then a considerable number of cases have been demonstrated in various continents, and a variety of names have been applied to it. I think Colcott Fox's appellation of this entity, namely, ringed eruption, is as good as, if not better than Crocker's, for this condition is not a true granuloma.

I have seen an average of four cases a year in the past 25 years. Apparently it is not a disease restricted to the poor, for I have seen more cases in private practice than in the clinics.

The etiology being unknown, therapy has been more or less whimsical. Radcliffe-Crocker originally used a mercurial plaster in which carbolic acid was incorporated. Local therapy was used most often—iodine tincture, iodine ointment, sulfur, and salicylic acid compounds. Radiotherapy and carbon dioxide snow allegedly produced disappearance of the lesions in reported cases. It is startling to see lesions of several months' duration disappear after a single biopsy. This fact apparently suggested to Robinson (Treatment of Granuloma Annulare; Clinical Note; A. M. A. ARCH. DERMAT. & SYPH. **67**:320 [March] 1953) the value of multiple incision.

Systemic medication has been tried by several authors, starting with bismuth, sodium aurothiosulfate, calciferol, and other drugs given parenterally or orally. Cochrane (Granuloma Annulare; Treatment with Vitamin E, *Brit. J. Dermat.* **62**:316-318 [July-Aug.] 1950) treated 13 patients with Ephynal (*dl*-alpha-tocopherol acetate), with a cure in 9 cases. I used it in two cases, without success, because the patients were unable to stand the expense after several months' therapy.

Most of these eruptions, however, disappear spontaneously without therapy. Nevertheless, some persist for years. I have followed one patient who has had lesions for five years. Inasmuch

as the eruption is often on the exposed areas of the skin, patients expect therapy. We should, therefore, all be grateful to Dr. Welsh for outlining a safe therapy that has produced such excellent results.

Dr. Eugene F. Traub, New York: Granuloma annulare is not only a disease of unknown causation but appears at times in decidedly varying clinical pictures. Furthermore, lesions appear and disappear, frequently without apparent reason, making evaluation of therapy difficult. I am sure we have all seen patches disappear following the performance of a simple biopsy. In fact after removal of a biopsy specimen, other lesions distant from the site may spontaneously resolve, and not return. The results of therapy are almost as good after treatment with the physical modalities, x-ray or solid carbon dioxide. Even heavy metals such as bismuth have been used with some success. Nevertheless, Dr. Welsh has presented a more specific response, wherein he may be directly influencing the cause of granuloma annulare. In his cases, as he points out, the best proof of relationship of the response to the specific therapy is the fact that when treatment was discontinued, relapses occurred, and when therapy was again resumed, clearing of the lesions again occurred. Keeping the patients on a maintenance dosage also kept them well, further proof that some relationship to the therapy must exist.

Welsh assumes that he stimulates a cortisone-like response with vitamin E, and the calcium pantothenate may be an additional biological catalyst also aiding the formation of new cortisone-like materials. Safety of the drugs used over long periods is emphasized because it is assumed that such natural stimulation of the adrenal gland would involve no stress. If Dr. Welsh is correct in his premise of this therapy acting through the adrenal gland, and in this premise he is certainly supported by the endocrine literature, I wonder whether the same effect could be obtained equally safely and more simply by giving small injections of corticotropin (ACTH) for a very short period of time.

Granuloma annulare may be an allergic response to bacteria. Corticotropin (ACTH) controls the clinical symptoms of allergic rhinitis, bronchial asthma, urticaria, and atopic dermatitis. After withdrawal of the hormone, the symptoms recur inevitably in the same shock tissue. Accordingly, according to Sampter, additional factors independent of the pituitary-adrenal regulation determine the site of the shock reaction in the allergic person. The tissue has somehow been caused to display excessive inflammatory and proliferative activity, which in the case of the persistent lesion leads to accumulation of cellular debris at the site of the allergic reaction. It is my understanding that both corticotropin (ACTH) and cortisone act to relieve the inflammatory phase of this reaction, while the tocopherols (Vitamin E) act as scavengers to clear up and remove cellular debris. With this in mind, possibly Dr. Welsh's results are not due to induced cortisone-like action, but rather are obtained through a much improved mechanism for tissue waste removal. The combination of calcium pantothenate with vitamin E may hasten the latter's normally sluggish action.

The case of the patient presented herewith on the screen was one shown recently before the New York Dermatological Society, where the diagnosis of granuloma annulare was accepted and the histology was confirmatory. This woman who had a widespread eruption involving extensively both arms, back and abdomen first presented discrete papular lesions which subsequenty became confluent, forming large annular and crescentic-shaped patches. The eruption had developed while the patient was being treated for another dermatosis. The condition cleared up rather rapidly in the course of about three months and has not relapsed since the use of several small doses of x-rays of about 50 r and a few injections of corticotropin (ACTH) given for another purpose. It is interesting to note how promptly these lesions disappeared in what was an unusually widespread and involved case. Unfortunately I am not in a position to state whether the small amount of corticotropin (ACTH) was responsible for the prompt remission or whether the few treatments with the x-rays were the most important factor. Whatever is to be credited for the disappearance of the lesions, it occurred more promptly than was the case with most of Dr. Welsh's patients.

Dr. Louis H. Winer, Beverly Hills, Calif.: At the present time, I have at the County Hospital in Los Angeles, a patient whose condition was diagnosed on clinical examination as chronic discoid lupus erythematosus both by our staff and by her former dermatologists at the Charity Hospital in New Orleans.

This patient has an eruption on the neck and hands similar to a chronic lupus erythematosus. Two specimens were removed for biopsy and examined microscopically. But before we reported the histologic diagnosis, the patient was started on quinacrine (Atabrine) and she promptly improved. On histologic basis, our diagnosis was granuloma annulare on both specimens.

This suggests a similarity in the reaction to therapy of chronic lupus erythematosus and granuloma annulare. Likewise, there are similar histological changes; both conditions have perivascular mantling of an infiltrate and both conditions show fibrinoid degeneration of the collagen.

Dr. Ashton L. Welsh, Cincinnati: My reason for attempting use of this form of therapy in granuloma annulare was based on the fact which Dr. Winer has just emphasized—similarity in histological changes in patients with lupus erythematosus and granuloma annulare. My premise was: if patients with lupus erythematosus responded to massive doses of pantothenic acid derivatives combined with vitamin E (and I reported last year that they did so respond), then patients with granuloma annulare might also respond.

Since my tabulation of response, two more patients with granuloma annulare, on this form of therapy, have cleared completely. Therefore, the total number of patients who cleared is now 11, instead of 9. The last patient cleared completely in one month, and she had had the disease for seven years.

Dr. Wilson has requested a recapitulation of the dosage schedule. Daily dosage of pantothenic acid derivatives varied from 5 gm. in children to 10 gm. in adults. Daily dosage of vitamin E varied from 0.3 gm. in children to 1.25 gm. in adults.

With regard to the activity or changes which are actually produced by this type of therapy, there has been a great deal of recent work on pantothenic acid. In the body, pantothenic acid breaks down into pantethine, the Lactobacillus bulgaricus factor, and two other factors which are now known. These two factors, plus pantethine, constitute about 40% of "coenzyme A," which is important in metabolic functions and which may stimulate the adrenals to form the steroid hormones. Also, pantothenic acid, acting through the thalamus, may produce some stimulation of the pituitary and increase the output of the adrenocortical hormone. Hence, with pantothenic acid acting through "coenzyme A" (which is necessary for the biosynthesis of the adrenal steroids) and through the pituitary, we obtain two forms of stimulation to adrenal activity. It has been shown, very recently, in animals (and humans) on pantothenic-acid-deficient diets that the adrenals are less able to tolerate stress and that the ability to withstand stress conditions increases on high pantothenic-acid intakes. Also, that the ability of the adrenal to function under stress is almost in direct proportion to the amount of available pantothenic acid.

In the body, vitamin E breaks down into quinones and paraquinones, tocopherol and tocopheryl quinones and hydroquinones. These make up, essentially, the four-ring-structure of cortisone, and, according to recent work, some of which is not yet published, they may constitute the "building blocks" for the adrenal steroid hormones. What we are doing, then, is supplying the "building blocks" and stimulating the adrenal to increased activity.

I think this is a little more rational than "artificial" or "substitution" therapy with corticotropin (ACTH) or cortisone because, as you know, with any substitution therapy, when the substitute is withdrawn, you are right back where you started. With pantothenic acid derivatives combined with vitamin E, we are attempting at least, to make the adrenal do its own job, and not attempting to do the job artificially.

REFERENCES

1. Welsh, A. L.: Lupus Erythematosus: Treatment by Combined Use of Massive Amounts of Calcium Pantothenate or Panthenol® with Synthetic Vitamin E, A. M. A. Arch. Dermat. & Syph. **65**:137, 1952.

2. Welsh, A. L.: Lupus Erythematosus: Treatment by Combined Use of Massive Amounts of Pantothenic Acid and Vitamin E, A. M. A. Arch. Dermat. & Syph. **70**:181, 1954.

3. Michelson, H. W.: Remarks on Lupus Erythematosus: Symposium on Systemic Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **27**:433, 1952.

4. Jacobi, F.: Granuloma Annulare, in Jadassohn, J.: Handbuch der Haut- und-Geschlechtskrankheiten, Berlin, Julius Springer, 1931, Vol. 10, Pt. 1.

5. Haliwell, E. O., and Ingram, J. T.: Granuloma Annulare, Brit. J. Dermat. **47**:319, 1935.

6. Bernstein, J. C.: Necrobiosis Lipoidica Diabeticorum (Urbach): Comparison with Granuloma Annulare, Arch. Dermat. & Syph. **36**:282, 1937.

7. Bolt, A.: Beitrag zur Klinik und Ätiologie des Granuloma Annulare, Arch. f. Dermat. u. Syph. **179**:603, 1939.

8. Ellis, F. A.: Necrobiosis Lipoidica: A Form of Granuloma Annulare? Arch. Dermat. & Syph. **43**:822, 1941.

9. Prunty, F. C., and Montgomery, H.: Granuloma Annulare, Arch. Dermat. & Syph. **46**:394, 1942.

10. Michael, J. C.: Etiology of Granuloma Annulare with Special Reference to the Tuberculous Theory, Arch. Dermat. & Syph. **29**:189, 1934.

11. Bruce-Jones, D. B. S.: A Case Clinically Resembling Morphoea with a Tuberculous Background and Indeterminate Histology Suggestive of Necrobiosis Lipoidica, Brit. J. Dermat. **49**:238, 1937.

12. Montgomery, H.: Histopathology of Various Types of Cutaneous Tuberculosis, Arch. Dermat. & Syph. **35**:698, 1937.

13. Hildebrand, A. G.; Montgomery, H., and Rynearson, E. H.: Necrobiosis Lipoidica Diabeticorum, Arch. Int. Med. **66**:851, 1940.

14. Civatte, A.: Les Formes tuberculo-ulcéreuses et tuberculo-gommeuses du granuloma annulaire, Ann. dermat. et syph. **79**:387, 1952.

15. MacKenna, R. M. B.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1948.

16. Vissian, L.: Atypical Forms and Etiology of Granuloma Annulare, Ann. dermat. et syph. **8**:363, 1948.

17. Bowers, R. E.: Histology of Granuloma Annulare Compared with that of Necrobiotic Nodules of Rheumatoid Arthritis, Brit. J. Dermat. **61**:247, 1949.

18. Macleod, J. M. H., and Muende, L.: Practical Handbook of the Pathology of the Skin, Ed. 3, New York, Paul B. Hoeber, Inc., 1948.

19. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

20. McDonald, J. R., and Weed, L. A.: Limitations of Histopathologic Technics in the Diagnosis of Granulomas, S. Clin. N. America **32**:1235, 1952.

21. Goodman, M. H., and Ketron, L. W.: Granuloma Annulare: Report of Unusual Cases with Comment on the Histology of the Disease, Arch. Dermat. & Syph. **33**:473, 1936.

22. Hitch, J. M.: Necrobiosis Lipoidica Diabeticorum (Urbach and Oppenheim), Arch. Dermat. & Syph. **36**:536, 1937.

23. Costello, M. J.: Case for Diagnosis (Necrobiosis Lipoidica?), Arch. Dermat. & Syph. **42**:394, 1940.

24. McCreight, W. G., and Montgomery, H.: Cutaneous Changes in Lupus Erythematosus: Histopathologic Aspects with Special Reference to Vascular Changes, Arch. Dermat. & Syph. **61**:1, 1950.

25. Ormsby, O., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

26. Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949.

27. Sulzberger, M. B., and Wolf, J.: Dermatology: Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952.

28. Laymon, C. W., and Fisher, L.: Necrobiosis Lipoidica (Diabeticorum?), Arch. Dermat. & Syph. **59**:150, 1949.

29. Andrews, G. C.: Diseases of the Skin, Ed. 3, Philadelphia, W. B. Saunders Company, 1947, p. 378.

30. Sulzberger, M. B., and Baer, R.: The 1952 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1953, p. 158.

31. Burgess, J. F., and Pritchard, J. E.: Noduloulcerative Granuloma of the Legs, Arch. Dermat. & Syph. **57**:605, 1948.

32. Burgess, J. F., and Pritchard, J. E.: Tocopherol (Vitamin E) Therapy in Sclerosis of the Legs with Ulcer, Canad. M. A. J. **61**:247, 1948.

33. Burgess, J. F.: Vitamin E (Tocopherols) in the Collagenoses, Lancet **2**:215, 1948.

34. Cochrane, T.: Granuloma Annulare: Treatment with Vitamin E, Brit. J. Dermat. **62**:316, 1950.

35. Hagerman, G.: On the Use of Vitamin E in Dermatologic Practice, Acta dermat.-venerol. **31**:225, 1951.

36. Shwartzman, G., and Schneierson, S. S.: Inhibition of the Phenomenon of Local Tissue Reactivity by Corticosteroids, Salicylates, and Compounds Related to Salicylates, Ann. New York Acad. Sc. **56**:733, 1953.

37. Boe, J., and Stoa, K.: Adrenocorticotropin-like Effect of Acetylsalicylic Acid: Treatment with Acetylsalicylic Acid and Pantothenic Acid, Acta endocrinol. **12**:201, 1953.

38. Ellis, F. A., and Kirby-Smith, H.: Necrobiosis Lipoidica and Granuloma Annulare, Arch. Dermat. & Syph. **45**:40, 1942.

39. Galloway, J.: Lichen Annularis: A Ringed Eruption of the Extremities, Brit. J. Dermat. **11**:221, 1899.

40. Crocker, R.: Granuloma Annulare, Brit. J. Dermat. **14**:1, 1902.

41. Arnt, G.: Zur Kenntnis des Granuloma Annulare, Arch. Dermat. u. Syph. **108**:229, 1911.

42. Bacchus, H., and Heiffer, H. M.: Influence of Ascorbic Acid on the Metabolic Actions of Cortical Hormones, Am. J. Physiol. **172**:276, 1953.

43. Bacchus, H.; Altszuler, N., and Heiffer, M.: Prolongation of Effects of Adrenal Cortical Secretion by Ascorbic Acid: Proposed Mechanism of Action, Proc. Soc. Exper. Biol. & Med. **80**:88, 1952.

44. Eisenstein, A. B., and Shank, R. E.: Relationship of Ascorbic Acid to Secretion of Adrenocortical Hormones in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **78**:619, 1951.

45. Casentini, S.; Libretti, A., and Tusini, G.: The Histolochemical Characteristics and the Cholesterol and Ascorbic Acid Contents of the Adrenals in Animals Deficient in Pantothenic Acid, with or without Adrenocorticotropic Hormone (ACTH) Treatment, Arch. Internat. pharmacodyn. **92**:217, 1952.

46. Ershoff, B. H.: Comparative Effects of Pantothenic Acid Deficiency and Inanition on Resistance to Cold Stress in the Rat, J. Nutrition **49**:373, 1953.

47. Meites, J.: Counteraction of Cortisone Inhibition of Body, Hair and Thymus Growth by Vitamin B_{12} and Aureomycin, Proc. Soc. Exper. Biol. & Med. **78**:692, 1951.

48. Catron, D. V.; Bennison, R. W.; Maddock, H. M.; Ashton, C. C., and Homeyer, P. G.: Effects of Certain Antibiotics and Vitamin B_{12} on Pantothenic Acid, J. Animal Sc. **12**:51, 1953.

49. Granados, H., and Verzar, F.: Influence of Pantothenic Acid and Other B Vitamins on the Adrenalectomized Rat, Internat. Ztschr. Vitaminforsch. **24**:403, 1953.

50. Goldblatt, S.: Cyancobalamin (Vitamin B_{12}) Therapy of Lupus Erythematosus: Further Observations, Acta Dermat.-venereol. **33**:216, 1953.

SOUTH AMERICAN BLASTOMYCOSIS

Report of Case and Review of Laboratory Features

HAROLD O. PERRY, M.D.
LYLE A. WEED, M.D., Ph.D.
AND
ROBERT R. KIERLAND, M.D.
ROCHESTER, MINN.

AS CLINICIANS practicing medicine in the United States, we are apt to exclude from consideration as the cause of an obscure systemic fungous disease, the etiologic agent of South American blastomycosis. This disease peculiarly limits itself to the South American continent. Conant and co-authors, who have just recently published the second edition of their "Manual of Clinical Mycology,"[1] reported only one case from elsewhere, this being from Costa Rica. For the past 17 months we have had under our care a patient with South American blastomycosis from the state of Oregon. We are reporting our experience with this patient, for whatever help it may be to those called upon to handle this problem in the future.

REPORT OF CASE

A married white man, 32 years of age, had been in good health until 1949, when he noted slight shortness of breath on lying down. Later that year, during an insurance examination, a roentgenogram of the thorax showed small nodular densities throughout both midpulmonary fields. Physical examination revealed small tender lymph nodes in the cervical region bilaterally. He was given alternately courses of chlortetracycline (Aureomycin) and penicillin, with the result that after some months the lymphadenopathy subsided. The roentgenographic appearance of the lungs remained unchanged.

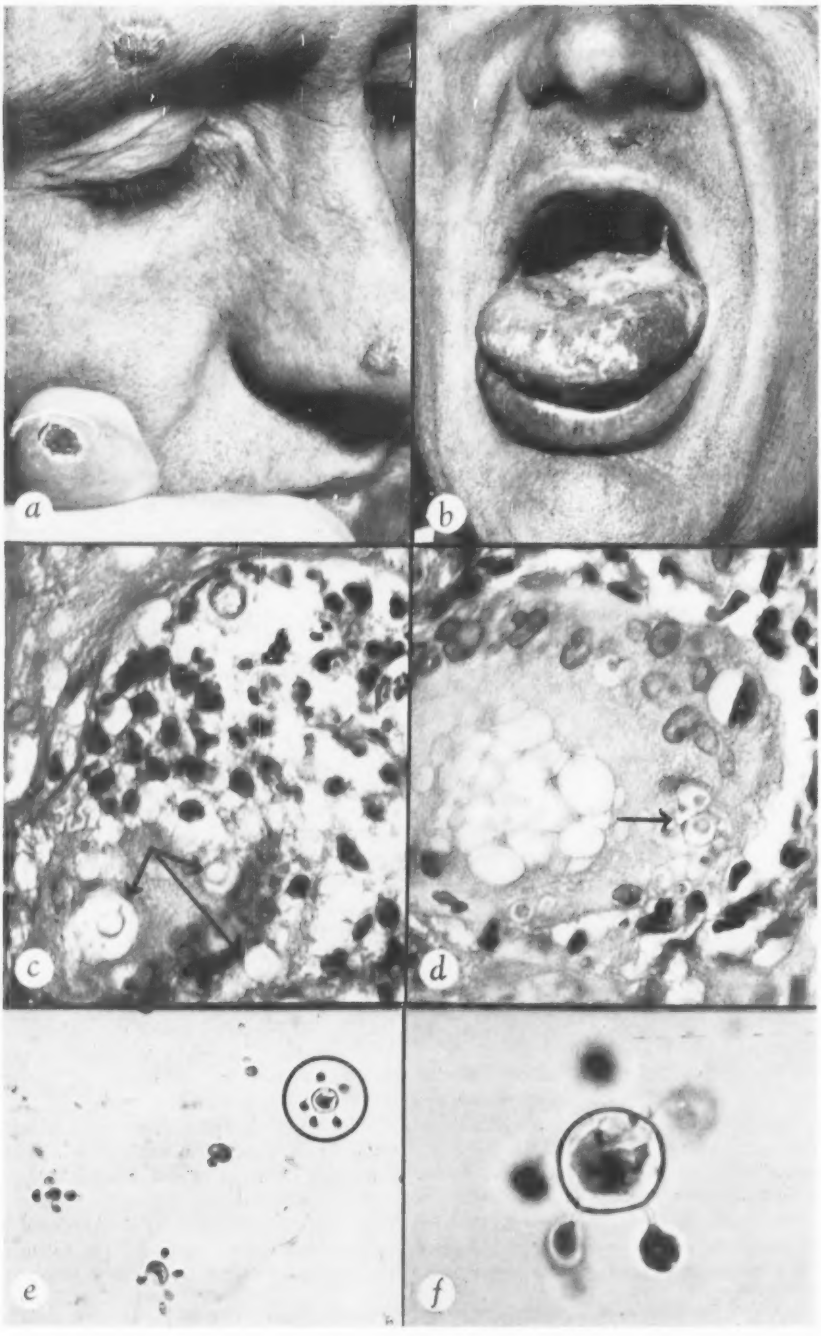
During 1950, a gradually increasing huskiness of the voice developed. There was some irritation of the throat, but no lesions were noted. Swab cultures of the oropharynx were said to have grown Staphylococci, and courses of Staphylococcus vaccine were given.

The soreness of the throat persisted, and by the summer of 1951 superficial white plaques developed on the tongue and buccal mucosa. The individual lesions fused so that the oral mucous membranes became confluently involved. At the same time, small crusted lesions developed over the forehead, the left thumb, and the right buttock. In November, 1951, biopsy of the involved site in the nasopharynx led to the diagnosis of blastomycosis. No cultures were made.

On the basis of the pathologic report, the patient was desensitized with Blastomyces dermatitidis vaccine during December, 1951, and subsequently was given potassium iodide orally. By the end of 1951, so much of his mouth was involved that eating caused great pain. By this time the patient had lost 45 lb. (20.4 kg.). He had marked generalized weakness.

The patient's health continued to deteriorate during 1952. The oral lesions continued to progress, with extension onto the lips. He was unable to talk above a whisper. The lesions of the forehead, thumb, and buttock increased in size. A single roentgen treatment was given to

From the Section of Dermatology and Syphilology (Drs. Perry and Kierland) and the Section of Bacteriology (Dr. Weed), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.



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each of the lesions of the forehead and thumb, without beneficial results. During the summer of 1952, a total of 70 intravenous injections of stilbamidine were given. The first dose was 150 mg., the remaining doses being 100 mg. each. In August, two days after the last injection, paresthesias of the middle branch of the fifth nerve developed bilaterally. Prior to this, in July, another biopsy had disclosed the presence of doubly contoured, rounded bodies of different sizes; with a single exception, no budding of these bodies was noted. A diagnosis of blastomycosis due to B. dermatitidis was made. Cultures of tissue taken at the time of biopsy failed to show growth of any organism.

At the completion of the stilbamidine therapy in August, 1952, oral courses of 20 gm. of chlortetracycline were given concomitantly with potassium iodide. Eighty minims (4.93 cc.) of a saturated solution of the latter was administered three times daily. For two and one-half weeks during October, 1952, the patient received, in addition, sulfisoxazole (Gantrisin).

The patient was first seen at the Mayo Clinic in November, 1952. Additional history indicated that he had been employed in Venezuela in 1946. During his sojourn in that country, he recalled, he had traumatized the left shin, and an ulcer with suppuration and crusting had developed at the site of injury; the ulcer had healed spontaneously after three or four months. No specific treatment had been given.

Physical examination showed marked wasting of the musculature, with generalized weakness. The patient weighed 140 lb. (63.5 kg.) whereas his usual weight was 210 lb. (95 kg.). It was difficult for him to walk because of pain in the right hip. Respirations were shallow and rapid. Deep breathing caused thoracic pain. He appeared to be in acute discomfort. This was caused primarily by a granulomatous plaque that involved the oropharynx, buccal mucosa, tongue and lips. The involved areas were sharply marginated by a rolled border. Bright red and yellowish puncta, less than 1 mm. in diameter, were seen scattered over the entire surface. The involved area was bathed in an excess accumulation of mucus (Fig. *b*). The mouth was held partially open, and there was a continual flow of secretions from the angles of the mouth. Nonspecific crusted ulcerations with no sign of punctate minute abscesses were seen scattered over the body. The largest of these, 1 cm. in diameter, was located in the right eyebrow (Figure *a*). Other smaller but similar lesions were noted overlying the occiput, in the right infraorbital area, on the right ala nasi, on the tip of the left thumb, and on the plantar surface of both feet. There was generalized minimal enlargement of the lymph nodes. Hepatosplenomegaly was not present.

Initial studies included a thoracic roentgenogram, which showed two small areas of fibrosis in the right lung and the right cardiophrenic angle anteriorly. The concentration of hemoglobin was 13.7 gm. per 100 cc. of blood; the erythrocytes numbered 5,230,000, and the leucocytes 5,400 per cubic millimeter, with a differential count of 27% lymphocytes, 55% segmented neutrophiles, 13% eosinophiles, 4% monocytes, and 1% basophiles. The sedimentation rate (Westergren method) was 47 mm. in one hour. A flocculation test for syphilis gave negative results. The results of blastomycin and histoplasmin skin tests were read as negative 48 hours after application. Urinalysis showed no abnormalities. A direct potassium hydroxide preparation of serous exudate from the ulcer of the right second toe showed a doubly contoured organism with a single small bud. A biopsy specimen from this lesion was subjected to histologic examination and culture; histopathologically, the diagnosis was simply blastomycosis. To exhaust the possibilities of laboratory investigation of the problem, cultures were also made from the ulcers of the right eyebrow and the left thumb, and from the sputum, blood, and urine.

Symptomatic therapy included a soft diet and mouth washes. In view of the already impaired function of the fifth nerve, it was decided to avoid stilbamidine in future therapy. Diethylstilbestrol

EXPLANATION OF FIGURE

South American blastomycosis. (*a*) The cutaneous lesions consisted of crusted superficial ulcerations. (*b*) The oral findings were those of erythematous granulomatous plaques studded with bright-red and yellow puncta. The surface of the tongue appeared not unlike the surface of a strawberry. (*c*) Numerous doubly contoured organisms, one of which suggests the presence of multiple budding (hematoxylin and eosin; × 800). (*d*) In some areas, oval or round bodies surrounded by a clear halo are noted (hematoxylin and eosin; × 800). (*e*) Smear from the primary isolation showing doubly contoured organisms with multiple buds (lactophenol cotton blue; × 400). (*f*) Enlargement of the encircled organism in Figure *e*, showing definite connection of the buds with the parent cell (lactophenol cotton blue; × 800).

was given initially in doses of 2 mg. twice daily and subsequently in doses of 3 mg. twice daily. On the 11th hospital day, 5 mg. twice daily was administered.

After 14 hospital days, the patient's condition was essentially the same as on admission. There had been no further loss of weight. The mouth was still acutely painful, and the skin lesions remained unchanged. Marked weakness was still noted. At this time, cultural studies had not yielded a positive result. The diagnosis of North American blastomycosis was questioned in view of negative cultures and failure of treatment in the past. Because no definite diagnosis had yet been made, a biopsy specimen from the lesion in the mouth was subjected to culture. Six days later, fine granular colonies were noted on the enriched blood agar incubated at 37 C. Smears from this growth revealed multiple budding forms characteristic of Blastomyces brasiliensis. Transfers from colonies in the yeast phase to enriched blood agar incubated at room temperature demonstrated the filamentous form of the organism. The roentgenographic appearance of the thorax, the results of urinalysis, the concentration of hemoglobin and the leucocyte count, including a differential count, were similar to those on admission.

Therapy was started with sulfadiazine, 1 gm. four times daily, administered with an equal amount of sodium bicarbonate. Five days later, the patient was dismissed from the hospital to continue treatment with 10 mg. of diethylstilbestrol and 4 gm. of sulfadiazine a day.

Examination four days after dismissal from the hospital revealed no clinical changes in any of the mucous membrane or cutaneous lesions. The patient recognized, however, that all lesions were less painful. Fully clothed, he weighed 156 lb. (70.8 kg.), whereas his last weight in the hospital was 141½ lb. (64.5 kg.).

During the next seven days the patient noted lessening of pain in the mouth. This permitted him to eat and satisfy his ravenous appetite. His weight was now 166 lb. (75.3 kg.), a 10-pound (4.5 kg.) gain over that of the previous week.

Cultural studies were repeated at this time, after 11 days of sulfadiazine therapy. The cultures of the sputum and scrapings from the tongue were subsequently reported as showing the growth of B. brasiliensis. Those from the ulcer of the right eyebrow, previously mentioned, were negative for any evidence of growth. The patient was dismissed to his home to be followed by the referring physician. Approximately six weeks after dismissal, the patient wrote that the lesions of the skin and mucous membrane had practically healed. He then weighed 186 lb. (84.4 kg.) and was employed full time. His voice had become normal.

Six months after dismissal, the patient informed us that he had discontinued all medication because of severe gastrointestinal upsets. He had no complaints except slight deafness in the right ear. His weight was 205 lb. (93 kg.).

The patient was next seen in January, 1954, some 14 months after the first examination. His weight of 210 lb. (95 kg.) had been maintained for the past several months. He had been working daily, doing heavy labor. His only complaint was that of aphonia which began again abruptly in September, 1953. Speaking above a whisper was now impossible. No cutaneous lesions were present. Two small hypertrophic plaques, each about 5 mm. in diameter, were noted at the tip of the tongue. A number of similar lesions were present on the buccal mucosa near the right angle of the mouth.

The urine, the concentration of hemoglobin, the erythrocyte and leucocyte counts and the erythrocyte sedimentation rate were normal. A roentgenogram of the thorax revealed only the apical fibrosis noted a year previously.

A biopsy specimen from the mouth was interpreted histologically as showing South American blastomycosis. Cultures from a tissue specimen from the right cheek subsequently showed the presence of B. brasiliensis, while cultures of the urine, from which B. brasiliensis had been grown a year previously, failed to show such growth on this occasion.

COMMENT

Because of the infrequent occurrence of South American blastomycosis on the North American continent, American dermatologists are not as well acquainted with the clinical and laboratory features of this disease as they might otherwise be. As would be expected, most of the literature on this subject originates from South America. Furtado, Wilson, and Plunkett [2] have reviewed this disease in its entirety.

Our study of this case brought out several features of the disease which bear emphasis in the evaluation of future cases. A history of trauma was elicited only after such information was sought by direct questioning. We presume that the portal of entry for the organism was this site of injury. Furtado and co-workers expressed the opinion that the mucous membranes are the usual portal of entry and that tegumentary penetration is rare.

In any disease in which the etiologic agent can be cultured in the laboratory, every effort should be expended in this direction before the diagnosis is decided on less definite evidence. The direct microscopic examination of a potassium hydroxide preparation of skin scrapings or pus often is of great help in determining the direction future cultural studies should take. But an etiologic diagnosis cannot be made solely on the basis of such an examination. Our own preliminary examination by this method revealed a doubly contoured, singly budding organism that was thought to be typical for B. dermatitidis. The clinical picture and lack of response to medications used for North American blastomycosis made us doubt the validity of our original observation; hence our extensive cultural investigation was undertaken.

Tissue sections likewise should be very critically evaluated. Fungi seen in histologic sections indicate definitely that a mycotic disease is present; final decision as to the exact type should await cultural studies. The difficulty of classifying a specific mycotic organism seen microscopically in tissue sections has been reviewed recently by one of us (Weed).[3]

In our case, the specimen removed for biopsy was the site of epithelial hyperplasia and microabscesses with a few thick-walled spherical organisms, some of which showed a suggestion of multiple budding (Figure *c*). In addition, some of the giant cells contained small oval or spherical bodies 2 to 4 μ in diameter and surrounded by a clear halo, closely resembling the features seen in histoplasmosis (Figure *d*). Since structures with definite multiple buds were not found, it was impossible to determine on a histologic basis alone whether this was infection with B. dermatitidis showing the so-called large and small forms,[4] B. brasiliensis showing phagocytized buds or gemmules as small forms, Histoplasma capsulatum showing the giant forms described by Schwarz,[5] or a mixture of B. dermatitidis and H. capsulatum.

B. brasiliensis grows more slowly than B. dermatitidis, either at 37 C. or at room temperature. Our experience has been that, in general, Blastomyces, like Histoplasma, is quite a fastidious organism on primary isolation, and some strains may not grow at all on conventional Sabouraud or ox-gall media which are frequently used for this purpose. Once the organisms have become adapted to laboratory conditions, however, they may grow fairly well on these media. In a fair percentage of our cases of blastomycosis and histoplasmosis, positive cultures have been obtained on fresh-meat-extract blood agar with glucose when cultures from aliquot portions of the material on Sabouraud or ox-gall media have been negative.

On enriched blood-agar medium, cultures made from the biopsy specimen from the lip in the present case showed numerous finely granular colonies on the 6th day of incubation at 37 C., while cultures on the same type of medium held at room temperature (24 C.) began to show filamentous colonies on the 11th day. In the smears of colonies grown at 37 C., there were numerous multiple budding forms characteristic of B. brasiliensis (Figure *e* and *f*). Cultures incubated at 30 C. grew

almost as rapidly as those at 37 C., and the organisms were in the yeast phase. Cultures of the tissue removed from the cheek for biopsy on the return visit (one year after the first visit) showed the same features. It is apparent that if cultures are to be made of tissue removed for biopsy with the intent of isolating Blastomyces, more rapid and more reliable results will be obtained if many of the conventional media used for isolating fungi are replaced with the more suitable medium described herein.

There is still some controversy as to the value of the sulfonamide drugs in the treatment of South American blastomycosis. The improvement noted in the well-being of this patient followed the institution of sulfadiazine treatment. The cause-and-effect relationship was unmistakable. Our own experience substantiates the viewpoint that sulfadiazine is of value as a suppressive agent in this disease. Although the patient had a satisfactory clinical course, failure of sulfadiazine to cure the disease is evidenced by the fact that tissue cultures were positive for B. brasiliensis a year later. Although stilbamidine is of value in the treatment of North American blastomycosis, it was of no apparent benefit in our case of South American blastomycosis.

SUMMARY AND CONCLUSIONS

A case of South American blastomycosis is reported. It is emphasized that a diagnosis of this type of blastomycosis should be confirmed by culture studies. Potassium hydroxide preparations and tissue sections may give suggestive evidence of the disease but they alone may offer an inadequate basis for a definite diagnosis. Laboratory study of the disease is discussed from the standpoint of cultural techniques and differential diagnosis of histologic sections. In this case, the value of treatment with sulfadiazine was evident. The improvement brought about by this drug is not to be interpreted as a cure but rather as a temporary suppressive effect only.

REFERENCES

1. Conant, N. F.; Smith, D. T.; Baker, R. D.; Callaway, J. L., and Martin, D. S.: Manual of Clinical Mycology, Ed. 2, Philadelphia, W. B. Saunders Company, 1954.

2. Furtado, T. A.; Wilson, J. W., and Plunkett, O. A.: South American Blastomycosis or Paracoccidioidomycosis: The Mycosis of Lutz, Splendore, and Almeida, A. M. A. Arch. Dermat. & Syph. **70**:166-180 (Aug.) 1954.

3. Weed, L. A.: Large and Small Forms of Blastomyces and Histoplasma, Editorial, Am. J. Clin. Path. **23**:921-923 (Sept.) 1953.

4. Manwaring, J. H.: Unusual Forms of Blastomyces Dermatitidis in Human Tissues, Arch. Path. **48**:421-425 (Nov.) 1949.

5. Schwarz, J.: Giant Forms of Histoplasma Capsulatum in Tissue Explants, Am. J. Clin. Path. **23**:898-903 (Sept.) 1953.

EFFECT OF LOCAL ADRENOCORTICAL HORMONES ON CUTANEOUS SPREADING

F. B. BENJAMIN, D.M.B., Ph.D.
AND
THEODORE CORNBLEET, M.D.
CHICAGO

THE PATTERNING of eruptions, the response of the skin to infection, and many other facets of cutaneous behavior depend upon the changing and changeable barriers and fairways within this organ. A few imperfectly known and probably many unknown factors control this state of flux. These recently intensively studied phenomena are now generally known under the collective term of spreading. We now know several factors for influencing the latter, and one of them is the balance of hormones. In this it is believed the adrenocortical group plays a leading role. The present study shows the effects of locally placed adrenocortical hormones * on spreading of materials within the skin.

The influence of adrenocortical hormones on the intradermal spreading of dyes was first examined by Opsahl in 1949.† She found that in the rabbit locally and intravenously administered adrenocortical extract inhibited cutaneous spreading. Winter and Flataker [5] observed a similar effect in mice and rats. Benjamin, Cornbleet, and Grossman [1] found in human experiments that intradermal spreading of dyes was markedly increased by the addition of desoxycorticosterone acetate, and it was slightly decreased by cortisone.

Our past work was restricted to animals and to healthy young men. In view of the fact that adrenocortical activity is markedly changed in various pathological conditions, it was decided to determine the normal and hormonal spreading pattern under various pathological conditions.

METHOD

In all tests 0.1 cc. of a 2% solution of trypan blue in saline was injected intradermally in the upper part of the subject's back. The hormones, 5 mg. per cubic centimeter, were used in their commercial suspension medium. Spreading was determined 24 hours after injection.

RESULTS

Table 1 indicates that with the saline-dye solution there may be a decrease of spreading in chronic degenerative diseases and an increase of spreading in collagen diseases. None of these changes are significant in this series.

From the Departments of Clinical Science and Dermatology, University of Illinois College of Medicine and the Cook County Hospital.

* Cortisone acetate was supplied by Merck & Company, Inc. and by the Upjohn Company. Desoxycorticosterone acetate (Percorten) was supplied by Ciba Pharmaceutical Products, Inc.

† References 2, 3, and 4.

Also in Table 1 is shown the effect of cortisone on this spreading pattern, and it is seen that in the control group the addition of cortisone decreases spreading. This effect is reversed in malignant tumors and in collagen diseases, and it is restored to normal again after corticotropin (ACTH) therapy in disseminated lupus erythematosus. In Table 2, the same series is presented in a different way, by giving the number of subjects in each group in whom the addition of the hormone caused an increase or a decrease over the saline spreading of the same subject. Here we note the same differences as in Table 1 but also the exceptions to this pattern of

TABLE 1.—*Intradermal Spreading* of Trypan Blue Two Per Cent in Isotonic Sodium Chloride*

No. of Subjects	Diagnosis	Saline	Cortisone	Desoxycorticosterone Acetate
10	Control	16.3 ± 0.9	12.1 ± 1.3	22.5 ± 1.9
34	Various chronic diseases †	15.8 ± 0.7	12.9 ± 1.1	20.8 ± 2.1
18	Malignant tumors ‡	15.5 ± 0.8	17.8 ± 1.2	18.7 ± 1.8
24	Collagen diseases §	16.8 ± 0.8	18.3 ± 1.1	19.9 ± 1.7
4	Disseminated lupus erythematosus	17.1	18.9	17.8
3 ‖	Disseminated lupus erythematosus after corticotropin	15.0	12.7	19.5
87	Total			

* The spreading after 24 hours is given as the mean diameter in mm.
† Tuberculosis, cardiovascular disease, gastrointestinal disturbances, and blood dyscrasias.
‡ Biopsy proved.
§ Rheumatoid arthritis, polyarteritis, dermatomyositis, and scleroderma.
‖ Two of these cases are also in the preceding group.

TABLE 2.—*Effect of Cortisone and Desoxycorticosterone Acetate on Intradermal Spreading*

No. of Subjects *	Diagnosis	Cortisone, 5 mg. per cc.		Desoxycorticosterone Acetate 5 mg. per cc.	
		Increase	Decrease	Increase	Decrease
10	Control	1	9	10	0
34	Various chronic diseases	6	28	31	3
18	Malignant tumors	14	4	16	2
24	Collagen diseases	19	5	22	2
4	Lupus erythematosus	3	1	2	2
3	Lupus erythematosus after corticotropin	0	3	3	0

* The figures give the number of subjects in whom the addition of the hormone caused an increase or a decrease over the saline pattern.

cortisone spreading. The reasons for these exceptions are unclear to us at present. Apparently they are not due to experimental errors because in some cases the tests were repeated several times and the results remained essentially unchanged. In the columns farthest to the right the effects of desoxycorticosterone acetate are shown. Table 1 shows in all groups an increase with desoxycorticosterone acetate over that of the saline alone, but the group differences of this increase are not significant.

Table 2 shows that there are again exceptions to this general reaction pattern. After repeating these tests we came to the conclusion these exceptions may be due to experimental error.

In addition to the above series we observed the effect of hydrocortisone in eight patients with collagen diseases. Only cases were selected in which cortisone caused

Fig. 1.—Cortisone (Compound E) decreases the spread of trypan blue in the normal skin; desoxycorticosterone acetate (DCA) increases it.

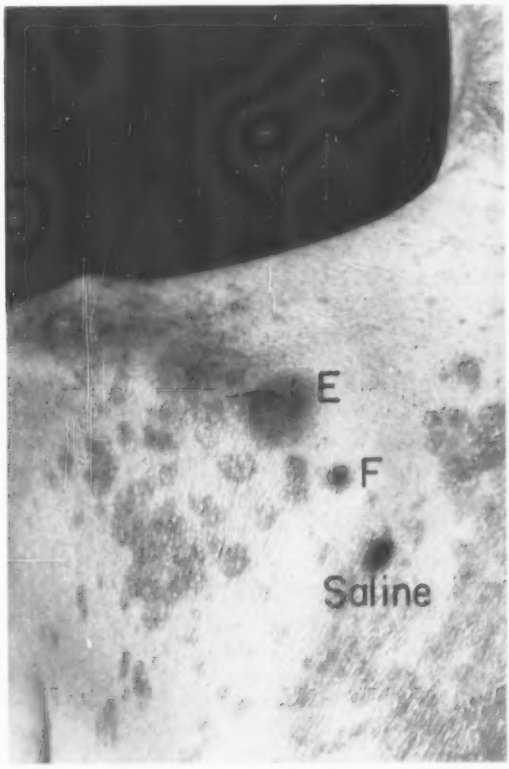

Fig. 2.—Cortisone (Compound E) increases the spread of trypan blue in systemic lupus erythematosus; hydrocortisone (Compound F) decreases it.

a marked increase of spreading. In these hydrocortisone caused a marked decrease in all cases. Figure 2 shows a patient in this series with the spreading of trypan blue under the influence of cortisone, saline, and hydrocortisone.‡

If 0.05 cc. saline and dye, cortisone and dye, and hydrocortisone and dye are each dropped at separate places on blotting paper the spreading pattern of both hormones is larger than that of saline. This may indicate that the physical effect (perhaps decreased surface tension) of the hormones is shown. This is the effect of cortisone in the skin, where, presumably, when locally used it is blocked and prevented from being transformed to hydrocortisone. These results may be looked upon as indicating that increased spreading is a physical phenomenon, whereas decreased spreading, as with hydrocortisone, is a biological one.

COMMENT

If we assume that hydrocortisone is the peripherally active metabolite of cortisone these findings might have two interesting explanations:

1. The amount of hydrocortisone produced by local application of cortisone is considerably less than the amount available by direct introduction of hydrocortisone. Thus, the difference of action is one of concentration.

2. In "collagen diseases" the conversion of cortisone to hydrocortisone may be blocked, or enzymes are lacking to effect the change.

It is not considered justifiable to draw further conclusions at present. Further study, however, may lead to a better understanding of the way these hormones act therapeutically.

Sulzberger § thinks it probable that there are absent in the skin activators which change cortisone into something locally effective, or that there are present in the skin cortisone-inactivators which inhibit the local beneficial effects. He implied he possessed supporting data for this belief. The local effectiveness of hydrocortisone as against the failure of cortisone would seem to confirm further hydrocortisone's peripheral mediating action for cortisone. In the normal person cortisone decreases spreading. If we assume such subjects possess activators for cortisone in the skin, then it would seem our patients with collagen disease had insufficient amounts or none at all of such facilitating materials. Thus cortisone increased spreading in such patients, while hydrocortisone decreased it, just as it does in normal subjects.

SUMMARY

1. As compared to normal subjects, there appears to be a tendency of decreased spreading of a saline solution of trypan blue in chronic degenerative diseases and an increase in collagen diseases.

2. Cortisone tends to decrease intradermal spreading, but this tendency is reversed in patients with malignant tumors and patients with collagen diseases. In three cases of disseminated lupus erythematosus under treatment with corticotropin, cortisone-spreading changed and approximated that for normal persons.

3. Desoxycorticosterone acetate causes in almost all cases an increase of spreading, and this result is not influenced one way or another by pathological conditions.

‡ Hydrocortisone was supplied by G. D. Searle & Company [Fadrenal] and by Merck & Company, Inc.

§ Sulzberger, M. B., in discussion on Hitch.[9]

4. Hydrocortisone decreases spreading even when cortisone causes an increase, as in patients with collagen diseases. This may indicate hydrocortisone is the mediating or effector substance formed from cortisone, and that the skin may have blocking agents to prevent the conversion of cortisone to hydrocortisone or be lacking in activator substances to effect this change.

REFERENCES

1. Benjamin, F. B.; Cornbleet, T., and Grossman, M. I.: Effect of Intradermal Injection of Adrenocortical Hormones, J. Invest. Dermat. **19**:109, 1952.

2. Opsahl, J. G.: Influence of Hormones from the Adrenal Cortex on the Dermal Spread of India Ink with and without Hyaluronidase, Yale J. Biol. & Med., **21**:255, 1949.

3. Opsahl, J. G.: Influence of Hormones from the Adrenal Cortex on Dermal Spread of India Ink with and without Hyaluronidase, Yale J. Biol. Med. **21**:487, 1949.

4. Opsahl, J. G.: Role of Certain Steroids in Adrenal-Hyaluronidase Relationship, Yale J. Biol. & Med. **22**:115, 1949.

5. Winter, C. A., and Flataker, L.: Influence of Cortisone and Related Steroids upon Spreading Effects of Hyaluronidase, Fed. Proc. **9**:137, 1950.

6. Hitch, J. M.: Action of Cortisone on Skin of Experimental Animals: Investigations on Protection Against Several Types of Injury to the Skin, A. M. A. Arch. Dermat. & Syph. **68**:256, 1953.

SYNDROME OF PEUTZ (MELANOPLAKIA AND SMALL INTESTINAL POLYPOSIS)

Observations with Special Reference to the Oral Pigmentation

MILLARD A. TROXELL, M.D.
CEDAR RAPIDS, IOWA

MELANOPLAKIA—a brown-black oral mucosal pigmentation—is literally a "black plate," and by definition the pigment need not be melanin. It has been described under various terms but most probably is a lentigo. Although opinions differ, the red free margins of the lips are herein considered as mucous—rather than cutaneous—surfaces.

Melanoplakia is physiologic in Negroes, frequent in yellow and brown races, and relatively frequent in white persons with "dark" complexion. It also has been associated with (1) local factors—including heavy metals, foods, dental abnormalities, foreign bodies, dyes, acids, gases, and drugs; (2) radiant energy, especially in the ultraviolet range; (3) malignant growths, including Hutchinson's lentigo maligna—7% of malignant melanomas arise from an initial lesion in the oral mucosa; (4) systemic diseases—including Addison's disease, cachexia, carcinomatosis, diabetes, hemochromatosis, hyperthyroidism, tuberculosis, malaria, Niemann-Pick disease, hepatic diseases, pancreatic diseases, gynecologic diseases, and rarely pernicious anemia, pellagra, sprue, and Gaucher's disease, and (5) dermatologic diseases, especially those with marked cutaneous pigmentation.* During the past two years I have observed melanoplakia in white adults with acromegaly (1), Addison's disease (2), erythroderma (2), neurofibromatosis (4), systemic lupus erythematosus (2), and porphyria (2). In addition, I have observed it in approximately 30 white patients with minor cutaneous disturbances.

In spite of recent advances, cutaneous melanogenesis is not clearly understood. Briefly, cutaneous melanin is produced under appropriate stimuli (whether extrinsic, intrinsic, or a combination thereof) by special epidermal cells (whether preexisting or newly formed under such stimuli). In general this applies to oral melanogenesis, but a few points should be emphasized.

In 1903 Adachi reported his demonstration of pigmented dendritic cells in the clinically nonpigmented buccal mucosa.[11] In 1927 Becker † reported microscopic

Histopathologic studies of the intestinal lesions were made by J. F. Noble, M.D., Director, Department of Pathology, Ancker Hospital.

Formerly, medical fellow, the University of Minnesota, Division of Dermatology, H. E. Michelson, M.D., Director, and Ancker Hospital, St. Paul, Department of Dermatology, J. F. Madden, M.D., Director.

Abridgement of a portion of a thesis submitted by Dr. Troxell to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

* References 1 to 10.

† References 12 and 13 and personal communication to the author, May 16, 1953.

epidermal pigmentation in the clinically nonpigmented buccal mucosae in 74% of 53 unselected autopsies on white patients. He stated that dendritic cells can be expected in 70% of specimens taken from the buccal mucosa, and this is a close correlation. In 1948 he stated, and recently reaffirmed, that the only evidence of transference of melanin from melanoblasts to epithelial cells has been in the buccal mucosa. The oral vestibule (which includes the lips) and the epithelial hypophysis are derived from adjacent portions of the embryonic oral membrane.

Oral pigmentation has been stressed particularly in the congenital ectodermoses (neurocutaneous syndromes; phakomatoses). Although the syndromes of Albright, Fanconi, Laurence-Moon-Biedl, Marfan, and Vogt-Koyanagi—as well as others—might be included, the "phakomatoses" at least include the following ‡: (1) von Recklinghausen's neurofibromatosis; (2) Bourneville's tuberous sclerosis; (3) Sturge-Weber's cerebral and trigeminal angiomatosis; (5) Wilcox's melanomatosis of the skin and central nervous system; and (6) Peutz's syndrome of melanoplakia and small intestinal polyposis.

THE SYNDROME OF PEUTZ

The American medical profession has become aware of the Peutz syndrome largely as the result of the excellent work of Jeghers and his associates.§ As described, there are but two essential features: melanoplakia and small intestinal polyposis. Subsequent reports have attempted to establish additional criteria, such as an appropriate family history, the appearance of the pigmentation at birth or in early childhood, and the occurrence of pigmentation or polyps in other locations. While it is convenient to have such other findings, to insist upon any one would exclude cases reported and accepted as examples of the syndrome. For example, family histories have been lacking in many of the reports, and such cases have been considered sporadic.[20]

In 1896 Hutchison [21] recalled a report of the first case of this syndrome, but it was not until 1921 that Peutz [22] first recognized and described the syndrome. He reported a father, mother, seven children, and two aunts who showed pigmentation in the oral mucosa and skin; three of them had nasal and intestinal polyposis, and one had pigmentation in the rectum. In 1946 Touraine and Couder [23] reviewed the literature and reported 31 cases, including one of their own. In 1949 Jeghers and his associates || reviewed the literature and summarized the number of cases reported at that time as 22 proved, 5 probable, and 4 possible—10 of the cases being their own. In 1951 they stated, "Four additional cases have been seen since our last report" (presumably by them). Subsequent case reports ¶ bring the total number of cases to 38, provided one considers Jeghers' total as 26 and includes the case herewith reported.

REPORT OF A CASE

A 77-year-old white Norwegian man was seen at Ancker Hospital on March 3, 1952. He first noted pigmented spots on the lips, together with alternating constipation and diarrhea, in early 1950. He was—and had been—in remarkably good physical condition. His previous medical and family histories were not contributory. Two days after hospital admission he passed a

‡ References 14 to 16.
§ References 17 to 19.
|| References 17 to 19.
¶ References 20 and 24 to 31.

quantity of bright red blood by rectum, and proctoscopic examination revealed three polypoid lesions at the rectosigmoid junction. Microscopic examination showed irregular, deep-staining, nonmucous surface glands; mitotic figures were seen, but there was no infiltration. The pathologist's diagnosis was "malignant polyp of the rectum."

Preoperative roentgenograms were interpreted as showing ectasia of the aortic arch, an ulcer in the midportion of the base of the duodenal cap, diverticulitis of the colon, multiple renal calcifications, and Paget's disease of the bony pelvis. A combined abdominoperineal bowel resection was performed on March 28, 1952. There were no polyps in the distal segment, but numerous polyps were found in the proximal segment, and gross examination demonstrated many small polyps throughout the small intestine. A duodenal polyp was found instead of the duodenal ulcer predicted by the roentgenologist. A small portion of the operative specimen was preserved in a "deep-freeze" and later stained unsuccessfully with "dopa" and silver. A similar attempt previously reported [29] was also unsuccessful. However, no polyps could be demonstrated in the particular specimen saved. The pigmented spot in the upper lip was removed (Fig. 1) and serial microscopic sections were prepared. Pigment was observed in sections stained with silver and with hematoxylin and eosin, but was best demonstrated [32] by unstained, deparaffinized section (Fig. 2).

In summary, another case—probably the 38th—of oral pigmentation associated with small intestinal polyposis is reported. The following features are of special interest:

1. He is the oldest patient reported to date (77 years).
2. He is the first reported with a fair complexion.
3. He is probably the sixth reported to have supervening malignancy in a polyp.
4. He probably presents the greatest number of malignant polyps reported to date (4).
5. The duodenal polyp is noteworthy.

HISTOPATHOLOGY OF ORAL MELANIN PIGMENTATION

The normal buccal mucous membrane shows a slight degree of epidermal pigmentation, which is largely confined to dendritic cells in the basal layer. In Addisonian melanoplakia it occurs in nearly every cell of the basal layer, and extends to the surface largely in capping form.# The "vertical band formation" reported as characteristic of the syndrome of Peutz has not been microscopically confirmed, and might well be identical with Becker's capping form or the columnar arrangement which I have observed in physiologic melanoplakia (Fig. 3). The grossly stippled appearance reported in Peutzian melanoplakia * is certainly observed in physiologic melanoplakia (Fig. 4). Furthermore, Jeghers' biopsy was of a palmar lesion, and palmar lesions are not an essential part of the syndrome. Even if they were, it cannot be assumed that oral and cutaneous lesions would show a comparable histopathologic picture.

Are these pigmented spots ephelides, lentigines, or nevi? Cutaneous lentigines are reportedly distinguished from ephelides by an increased amount of pigmentation, increased number of dendritic cells and proliferation of the rete pegs,† and from nevi spili by the absence of nevus cells.‡ Such distinctions are doubtful in the oral mucous membrane, where a relatively great number of dendritic cells § and high papillae [37] are normal. Although not supported by biopsy, Pusey's prediction [38] that histologic examination would present a normal appearance except for pigment in an "abnormal" location is correct.

References 12 and 13.
* References 17 to 19.
† References 33 and 34.
‡ References 35 and 36.
§ References 12 and 13.

Fig. 1.—Melanoplakia in Peutz's syndrome. Compared with other photographs of Peutz's syndrome, the spots are few. A stippled appearance is seen in the clinically nonpigmented mucous membrane, as well as in the pigmented spots. A lesion in the upper lip had been removed prior to photography.

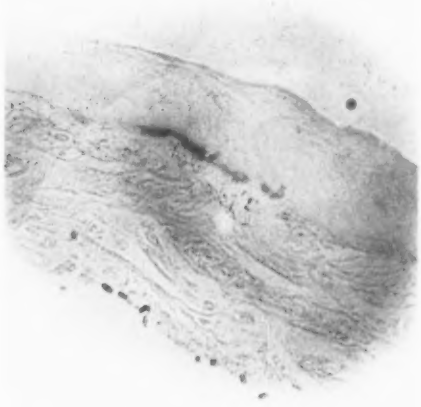

Fig. 2.—"Peutzian" melanoplakia. Photomicrograph of an unstained, deparaffinized section 30 μ thick; $\times$ 100; 560 mμ light filter. The pigment seems largely restricted to a well-demarcated portion of the basal layer. There is a marked variation in the degree of pigmentation within this portion. The dermal pigmentation largely underlies the epidermal pigmentation, and one might even postulate a zone of pigment transfer. This photograph provides histologic explanation of the clinical appearance, and rules out staining artifact.

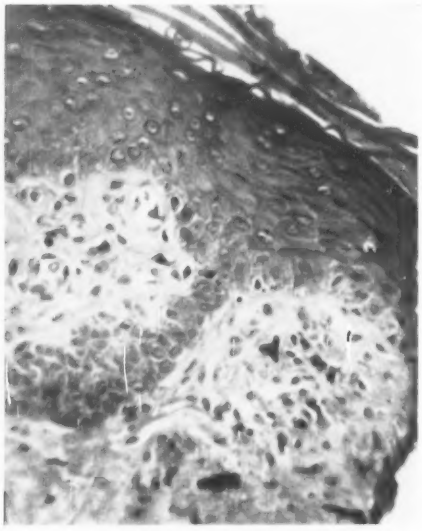

Fig. 3.—Physiologic melanoplakia. Photomicrograph from the lower lip at the moist-dry junction; section 6μ thick; hematoxylin and eosin; × 430; 540 mμ light filter. The patient is a healthy, fair-skinned, dark-haired, blue-eyed, 25-year-old white man of Swedish-American origin. Most of the basal cells contain pigment granules. The pigment granules also extend to the surface in a columnar formation from the top and sides of the papillae. The clear cells are increased in number, but not in proportion to the amount of pigment observed. There is irregular acanthosis and papillomatosis. Pigment-laden chromatophores are seen in the cutis.

Fig. 4.—Physiologic melanoplakia. The patient is a healthy, fair-skinned, dark-haired, blue-eyed, 28-year old white man of Swedish-American origin. In addition to the prominent spot on the lower lip, many smaller spots can be seen on both lips. Biopsy was not permitted.

Melanoplakia simply represents increased basal layer pigmentation. It may or may not show the following: downward proliferation of the rete pegs; significant increase in the number of clear cells; pigment granules in the upper epidermis—whether scattered, or extending to the surface in columns or bands; and pigment granules or clumps in the dermal chromatophores.

TREATMENT

Relatively few persons with melanoplakia are sufficiently concerned to seek medical attention. Those who do, however, are entitled to biopsy of the lesion in question; there have been several reports of malignant lesions which were benign in appearance, and of malignant transformation of previously benign lesions. An excision biopsy should be performed to forestall possible criticism, if for no other reason. This would exclude Pusey's recommended treatment by freezing for 10 seconds with solid carbon dioxide (which incidentally he had not employed),[38] and the application of 90% phenol followed after 20 seconds by 95% alcohol.[39]

The lesion should be excised with a small, curved scissors. Electrosurgery is then applied to the site, both to stop the hemorrhage and to diminish the possibility of recurrence. A small red spot may result, but this is less noticeable than the original lesion. This spot becomes less prominent or disappears completely within a year.

SUMMARY AND CONCLUSIONS

Pigmentation of the lip and other oral mucosae is often racial or physiologic.

Although adequate confirmation is lacking, the pigment is generally conceded to be melanin, which is produced by a special epidermal cell of undetermined origin.

A multitude of external or internal factors, or combinations thereof, may stimulate or influence the production of pigment.

The oral pigmentation is commonly unrecognized or disregarded by both patient and physician.

It is asymptomatic and may occur at any age.

It is rarely a direct diagnostic aid, but may indicate the need of search for gastrointestinal polyps.

Biopsy is advisable, followed by electrosurgery to the site of excision. The cosmetic results are excellent.

ADDENDUM

An additional case was reported after this paper was submitted for publication (Bruwer, A.; Bargen, J. A., and Kierland, R. R.: Surface Pigmentation and Generalized Intestinal Polyposis [Peutz-Jeghers Syndrome], *Proc. Staff. Meet., Mayo Clin.* **29:** 168-171 [March 24] 1954).

410 Iowa Theatre Building.

REFERENCES

1. Welsh, A. L.: Diseases of the Mucous Membranes, St. Louis, Educational Publishers, Inc., 1953.

2. Monash, S.: Normal Pigmentation of the Oral Mucosa, Arch. Dermat. & Syph. **26:**139-147 (July) 1932.

3. Dummett, C. O.: Physiologic Pigmentation of the Oral and Cutaneous Tissues in the Negro, J. Dent. Res. **25:**421-432 (Dec.) 1946.

4. Zinsser, H., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, Vol. 14, Pt. 1, pp. 1-67.

5. Darier, J.: Précis de dermatologie, Ed. 3, Paris, Masson & Cie, 1923, p. 388.

5a. Prinz, H., and Greenbaum, S. S.: Diseases of the Mouth and Their Treatment, Philadelphia, Lea & Febiger, 1935, pp. 409-420.

6. Dummett, C. O.: Abnormal Color Changes in the Gingivae, Oral Surg. **2**:649-669 (May) 1949.

7. Becker, S. W.: Skin: Melanin Pigmentation Produced by Physical Agents, in Glasser, O., editor: Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, pp. 1430-1432.

8. Allen, A. C., and Spitz, S.: Malignant Melanoma: A Clinicopathological Analysis of the Criteria for Diagnosis and Prognosis, Cancer **6**:1-45 (Jan.) 1953.

9. Nobl, G.: Zur Kenntnis oraler Pigmentationen, Wien. med. Wchnschr. **86**:729, 1926.

10. Anthony, H. G.: The Pigmentations of the Mucous Membrane of the Mouth, J. A. M. A. **51**:1685-1687 (Nov. 14) 1908.

11. Adachi, B.: Hautpigment beim Menschen und bei den Affen, Ztschr. Morphol. u. Anthrop. **6**:1-131, 1903.

12. Becker, S. W.: Melanin Pigmentation: A Systematic Study of the Pigment of the Human Skin and Upper Mucous Membranes, with Special Consideration of Pigmented Dendritic Cells, Arch. Dermat. & Syph. **16**:259-290 (Sept.) 1927.

13. Becker, S. W.: Dermatological Investigations of Melanin Pigmentation, in Biology of Melanomas, Special Publications, New York Academy of Sciences, 1948, Vol. 4, pp. 82-125.

14. Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, Arch. Neurol. & Psychiat. **26**:1145-1194 (Dec.) 1931.

15. Weber, F. P.: Some Considerations Connected with the Classification and Explanation of Naevi and Naevoid Conditions, Brit. M. J. **2**:992-994 (Oct. 27) 1951.

16. Wilcox, J. C.: Melanomatosis of the Skin and Central Nervous System in Infants, Am. J. Dis. Child. **57**:391-400 (Feb.) 1939.

17. Jeghers, H.: Pigmentation of the Skin, New England J. Med. **231**:181-189 (Aug. 3) 1944.

18. Jeghers, H.; McKusick, V. A., and Katz, K. H.: Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits, New England J. Med. **241**:993-1005 and 1031-1036 (Dec. 22 and Dec. 29) 1949.

19. Jeghers, H.; McKusick, V. A., and Katz, K. H.: The Syndrome of Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits, Ciba Clin. Symposia **2**:199-202 (July-Aug.) 1950.

20. Bradford, M. L., and Danzig, L. E.: Gastro-Intestinal Adenomatosis with Oral Pigmentation, Boston Med. Quart. **1**:21-24 (Dec.) 1950.

21. Hutchinson, J.: Pigmented Spots on the Lips, etc., in Twin Sisters, Arch. Surg. (London) **7**:290-291, 1896.

22. Peutz, J. L. A.: Very Remarkable Case of Familial Polyposis of Mucous Membrane of Intestinal Tract and Nasopharynx Accompanied by Peculiar Pigmentations of Skin and Mucous Membrane, Nederl. maandschr. geneesk. **10**:134-146, 1921; cited by Jeghers and associates.

23. Touraine, A., and Couder, F.: Lentiginose périorificielle et polypose viscérale, Presse Méd. **54**:405-406 (June 22) 1946.

24. Roux, J.: Lentigino-polypose digestive (syndrome de Peutz), Semaine hôp. Paris **26**: 2133-2139, 1950; abstracted, Excerpta Med. XIII, **5**:152 (March) 1951.

25. Perry, B. F., and Zuska, J. J.: Syndrome of Circumoral Pigmentation Associated with Generalized Intestinal Polyposis, U. S. Armed Forces M. J. **1**:773-777 (July) 1950.

26. Tanner, N. C.: Gastric and Jejunal Polyposis Associated with Melanin Spots of the Oral Region and Digits, Proc. Roy. Soc. Med. **44**:405-406 (May) 1951.

27. Wolff, H. H.: Familial Intestinal Polyposis with Pigmentation of Lips, Oral Mucosa, Face, and Digits, Lancet **1**:446-448 (March 1) 1952.

28. Schaffer, A. B., and Sahs, S. W.: The Syndrome of Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips, and Digits, Oral Surg. **5**:271-275 (March) 1952.

29. Lima Basto, E.: A Case of Polyposis of the Stomach and Small Intestine Associated with Pigmentation of the Face (Peutz Syndrome), Clin. contemp. **5**:494-504, 1951; abstracted, Excerpta Med. XIII, **6**:539 (Nov.) 1952.

30. Kitchin, A. P.: Polyposis of Small Intestine with Pigmentation of Oral Mucosa, Brit. M. J. **1**:658-659 (March 21) 1953.

31. Kaplan, I., and Feuchtwanger, M.: Recurrent Intussusception Due to Polyposis of the Gastro-Intestinal Tract Associated with Pigmentation, Brit. M. J. **1**:659 (March 21) 1953.

32. Troxell, M. A.: A Simple Aid in the Microscopic Detection of Melanin, J. Invest. Dermat. **22**:5-7 (Jan.) 1954.

33. Eller, J. J., and Eller, W. D.: Tumors of the Skin, Philadelphia, Lea & Febiger, Ed. 2, 1951, pp. 90-92.

34. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949, pp. 397-398.

35. Becker, S. W.: Pigmentary Diseases of the Skin, Clinics **3**:886-922 (Dec.) 1944.

36. Stegmaier, O. C., Jr., and Montgomery, H.: Histopathologic Studies of Pigmented Nevi in Children, J. Invest. Dermat. **20**:51-64 (Jan.) 1953.

37. Ham, A. W.: Histology, Philadelphia, J. B. Lippincott Company, 1950, p. 396.

38. Pusey, W. A.: Pigmented Spots of the Mucous Surface of the Lips, Arch. Dermat. & Syph. **36**:613 (Sept.) 1937.

39. Hirschfeld, I., and Hirschfeld, L.: Oral Pigmentation and a Method of Removing It, Oral Surg. **4**:1012-1016, 1951; abstracted, Excerpta Med. XIII, **6**:398 (Aug.) 1952.

ERYTHEMA ANNULARE CENTRIFUGUM (DARIER'S)

Clinical and Histologic Study

FRANCIS A. ELLIS, M.D.
BALTIMORE
AND
ASHER A. FRIEDMAN, M.D.
NORFOLK, VA.

COLCOTT FOX,[1] in 1891, under the title of erythema gyratum perstans, described an infrequent disorder of the skin of which the essential characteristic was persistent annular erythema. In 1908, Wende [2] assembled several cases and published, under the title of erythema figuratum perstans, a complete and detailed account of an entity characterized by persistent erythematous lesions with annular, circinate, and gyrate forms. Between 1891 and 1916, many writers described cases under different titles of which the essentiality was persistent annular erythema similar to, if not the same as, Wende's disease.

In 1916, Darier [3] described a persistent annular erythema under the title of erythema annulare centrifugum and maintained that it was a distinct entity, different from Wende's erythema figuratum perstans in that erythema annulare centrifugum was a "dry" disease, whereas Wende's erythema figuratum perstans showed evidence of vesiculation. Darier's title has become the more popular one for the persistent annular erythema group of diseases as evidenced by the titles of cases presented at dermatologic meetings. Since 1916, two new titles have appeared by Jadassohn [4] and Strempel [5] for diseases which seem to be clinically similar and are probably variants of Wende's and Darier's disease. There is another type of related disease described by Lipschütz [6] as erythema chronicum migrans, which we think may be distinct from the persistent annular erythema of Wende's and Darier's disease. Moreover, the etiology of Lipschütz's disease has been reported as being due to insect bite in several cases, whereas in the true persistent annular erythema of Wende and Darier the etiology is usually unknown.

In the cases described by Darier, there was no vesiculation, scaling, or lamination. Darier thus could not accept the cases of Wende and others, but the other features are so similar that they are all probably the same disease with slight clinical variations. Graham and Throne [7] in their article in 1930 described the vesicular type of Darier's erythema. Butler,[8] in 1932, gave a review of the literature on Darier's disease and presented a case.

Guichardot [9] reported two cases of erythema annulare centrifugum in 1951. In one patient the general physical findings were negative, and the other patient had pulmonary tuberculosis, but there may have been no association between the two

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diseases. Orbaneja and Vivancos,[10] in 1952, reported this disease in a 6-year-old boy and in making the differential diagnosis they considered the possibility of leprosy, but laboratory tests disproved this diagnosis. The biopsy showed vascular dilatation, with perivascular chronic infiltrate and with some edema in the papular and the subpapillary areas. Gammel [11] in 1952, reported a case of erythema gyratum repens (which apparently is a variant of erythema annulare centrifugum) associated with cancer of the breast. The eruption disappeared after treatment of the breast cancer.

Jillson and Hockelman,[12] in 1952, suggested that some forms of erythema annulare centrifugum are dermophytid reactions. They found that the chief pathologic characteristic was a focal infiltration of lymphocytes which was perivascular and periappendageal. We think that a superficial noninfiltrated type of erythema annulare centrifugum may occur as an dermophytid reaction to fungous infections of the hands and feet. Histologically, usually these reactions are so superficial that they do not show a very characteristic histologic picture. In addition there may be some inter-and intracellular edema of the rete cells with microscopic vesiculation of the epidermis. Stillians,[13] in 1953, discussed the occurrence of erythema annulare centrifugum with internal cancer and internal diseases. He stated that this disease may also be associated with mild infections. He did not discuss the histopathology.

The list of the different names given emphasizes the slight variants in the different authors' cases for this characteristic persistent annular erythema.

CLINICAL FEATURES

A diagnosis of erythema annulare centrifugum was made in 6 of 14,000 private patients, an incidence of slightly less than 4 in 10,000 patients, or approximately 1 in 2,400 patients.

Both sexes are affected, with a slightly increased incidence in the male. The disease seems to be one of the middle-age group, as 50% of the cases occurred in the 30- to 50-year group, although some of the cases reported started in early childhood. The average duration of the eruption is usually three years, some cases persisting 20 to 30 years, despite any and all modes of therapy. Bismuth, x-rays, and ultraviolet rays have been reported as giving fairly good results, but many cases are resistant to all forms of local and internal therapy.

The sites of the lesions are not confined to any particular area. The face, trunk, and extremities are affected, and in many cases generalization occurs. The trunk has been the site of predilection in our cases. There is no symmetry of lesions, and the hands and feet are rarely involved, in contrast to erythema multiforme.

The morphologic picture of erythema annulare centrifugum is that of a persistent erythema characterized by annular, circinate, gyrate, and serpiginous lesions. It commences as a small erythematous papule that enlarges slowly or rapidly, clears in the center and spreads peripherally to form well-defined annular lesions. The outer part of the advancing edge is erythematous and slightly raised, while the inner half usually is light yellow to brown and may have slight scale or desquamation and rarely superficial crusting. In some of the cases described by Wende and others (Klaber [14] as well as in some of our cases), minute vesicles and/or crusting may be seen on the advancing border. The annular lesions often coalesce to form gyrate, serpiginous, and bizarre zigzag lesions. Extension of the lesions is variable, but the

chronicity of the lesions with new ones forming as old ones are disappearing makes a characteristic picture. The plaques vary from 1 cm. to 50 cm. in diameter, with an active border 2 mm. to 1 cm. in width or occasionally wider.

Clinically, erythema annulare centrifugum must be differentiated from lupus erythematosus, chronic urticaria, erythema multiforme, fungous infection, granuloma annulare, leprosy, parapsoriasis en plaque (premycotic mycosis fungoides), early lymphomas, unusual forms of pityriasis rosea, and possibly other dermatoses.

HISTOLOGY

Lever [15] has suggested that histologically three cutaneous diseases may show a well-defined "collarette" infiltrate in the cutis. These are subacute and chronic discoid lupus erythematosus, secondary syphilis, and lymphoblastoma cutis.

Histologic Differentiation

	Epidermis	Dermis
Lupus erythematosus	1. Plugging 2. Atrophy 3. Edema, especially basal layer with liquefaction degeneration	1. Altered collagen—dilated capillaries 2. Dense perivascular and periappendigeal infiltrate; mainly small monocytes
Secondary syphilis	1. Usually shows moderate acanthosis 2. Mild edema 3. Some exocytosis	1. Collagen normal 2. Dense perivascular infiltrate; some diffuse lymphocytes; variable number of plasma cells
Lymphoma cutis	Essentially normal or atrophic	1. Collagen normal 2. Dense perivascular collections of lymphoma cells lymphocytes, monocytes, reticular cells.
Erythema multiforme	Edema to vesiculation	1. Collagen normal 2. Edema in upper Cutis; subacute infiltrate; lymphocytes, polymorphonuclear neutrophiles and eosinophiles 3. Nuclear debris
Erythema annulare centrifugum	Essentially normal or slight edema	1. Collagen normal 2. Dense perivascular infiltrate of small monocytes in relatively small nests or bands 3. No nuclear debris

While examining various slides from inflammatory dermatoses, we observed a well-defined collarette infiltrate consisting mostly of small mononuclear cells consistently occurring in sections from erythema annulare centrifugum.

In erythema annulare centrifugum, the epidermis is essentially normal. In spite of clinical evidence of scaling and occasionally superficial vesiculation, there may be in the latter cases only slight evidence of a dry crust or mild edema of the epidermis. Usually there is only a mild intracellular edema and no thickening or acanthosis of the epidermis. The striking features are in the cutis and the well-defined perivascular collarette infiltrate of small mononuclear cells which stands out in bold relief in an otherwise normal-appearing cutis. The collagen is not edematous and shows no tinctorial or morpholigic changes. The discrete perivascular infiltrate is located principally in the upper and middle cutis. This infiltrate may also be localized around the appendages, but this is not a striking feature.

HISTOLOGIC DIFFERENTIAL DIAGNOSIS

Histologically, erythema annulare centrifugum must be differentiated from chronic discoid lupus erythematosus, secondary syphilis, lymphatic leukemia cutis, and papular erythema multiforme. Lupus erythematosus can usually be ruled out by

epithelial changes, i. e., atrophy, plugging and—in the more acute forms—edema of the basal layer. The infiltrate in lupus erythematosus occurs in larger perivascular areas and is usually in well-defined periappendageal zones. The infiltrate consists of dense small mononuclear cells with an occasional reticulocyte. In contrast, in erythema annulare centrifugum the epidermis is essentially normal, and the infiltrate in the cutis occurs in smaller zones or bands and is less likely to be periappendageal. The infiltrate may seem to be less periappendageal in this disease because there are usually few hair follicles present and the infiltrate usually does not extend down to the zone that contains the sweat glands.

In early syphilis, especially in the papular forms, the epidermis also shows some involvement, with moderate increase in width and slight acanthosis, also usually mild evidence of edema and slight exocytosis. There is some perivascular cellular infiltration in the upper cutis as well as in the lower cutis. The infiltrate is composed mainly of small lymphocytes and, at times, a variable number of plasma cells. In papular secondary syphilis there is a "coat-sleeve" perivascular patchy infiltrate in the superficial and deep corium, and in addition there may be a diffuse scattering of cells. The infiltrate consists of lymphocytes and plasma cells, but the latter may not be sufficient in number to be of diagnostic significance. In lymphoblastoma, the infiltrate is usually denser, and only in the chronic lymphoid type is it composed purely of lymphocytic cells. Later one may see evidence of malignant growth in the variation of the type of cells or in the presence of mitosis. The lymphocytes seem to invade and grow between the collagen fibers.

In the histologic differentiation between erythema annulare centrifugum and erythema multiforme, only the papular and macular forms of the latter should have to be considered because in erythema annulare centrifugum, even when there is clinical or histologic vesiculation or crusting, one never sees the large vesicles or the evidence of edema which may occur in the vesicular or bullous forms of erythema multiforme. In fact, even in the papular form of erythema multiforme there is usually more evidence of edema in the epidermis and in the subepidermal layer of the cutis than in erythema annulare centrifugum. The infiltrate is polymorphous in erythema multiforme. In erythema annulare centrifugum the infiltrate consists mostly of small mononuclears, whereas in erythema multiforme one is likely to see besides the lymphocytes, a fair number of polymorphonuclears and eosinophiles. In erythema multiforme, there is usually some nuclear debris present in the infiltrate but there is usually no nuclear debris found in erythema annulare centrifugum. Histologically, in the very superficial type of erythema annulare centrifugum one may have to rule out such diseases as lichen striatus, toxicodermatoses and similar cutaneous diseases, but this applies only to the very superficial noninfiltrative forms.

REPORT OF CASES

CASE 1 (Figs. 1 and 2).—Mrs. M. M., aged 31 years, was first seen in November, 1948, complaining of an eruption which first appeared in 1946 on the body after a severe sunburn. When she was first seen by us, there were two large annular plaques in center of cheeks, with some smaller ones on the sides of her face and on her nose. In the last few weeks she had developed plaques on lower back and arms. The lesions on cheeks had an active slightly infiltrated border of about 1 cm., and seemed to show plugging, atrophy, and adherent scales. The patient's temperature was normal. The blood picture showed a mild leucopenia, 3,650 to 4,500, with a differential count of 33% polymorphonuclear neutrophiles, 56% lymphocytes, 5% eosinophiles, and 5% monocytes. Since 1948, patient was given many forms of local therapy plus injections

Fig. 1 (Case 1, Mrs. M. M.).—Annular configuration and the distribution of the lesions on the exposed areas similar to subacute disseminating lupus erythematosus.

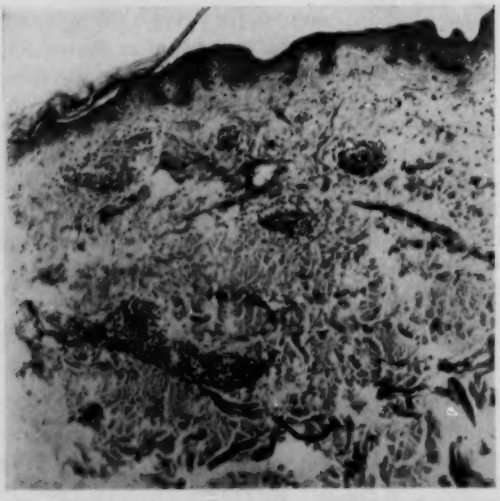

Fig. 2.—The epidermis is essentially normal. Extending throughout the dermis there is a perivascular infiltrate of small mononuclears in well-defined narrow bands (100 to 300 μ wide). Medium power; × 70.

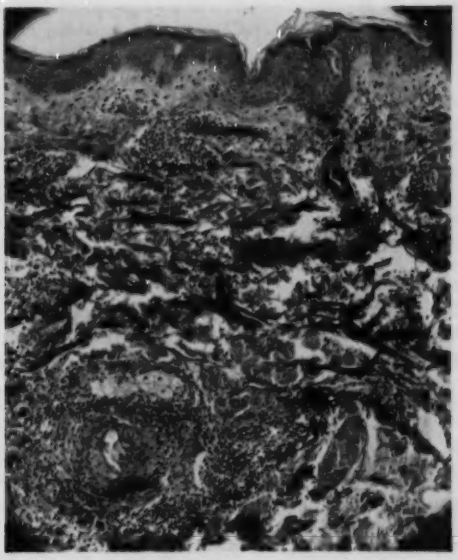

Fig. 3 (Case 2).—The epidermis is essentially normal. In the dermis there is a perivascular lymphocytic infiltrate extending about two mm. below the epidermis. Note the tendency of the lymphocytic infiltrate to form well-defined narrow bands or strands; × 100.

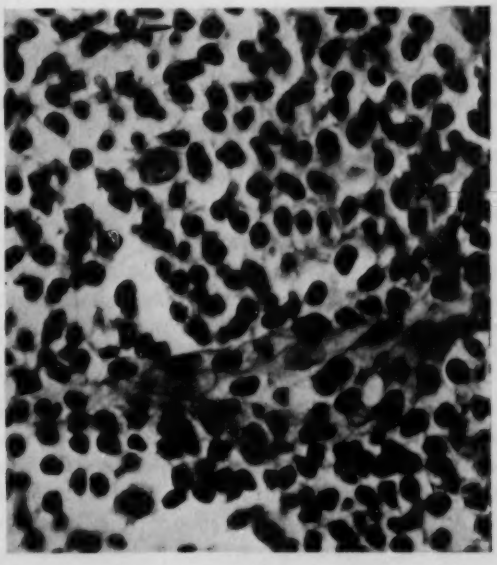

Fig. 4 (Case 2).—High power magnification. Shows in more detail the type of infiltrate consisting mostly of small mononuclears (lymphocytes) with relatively few reticuloendothelial cells.

of bismuth, mixed tocopherols, liver preparation, and vitamin B complex, but she continued to develop new lesions. Physical and laboratory findings were essentially negative. The eruption cleared completely, with no residual lesions during last trimester of her pregnancy in 1949 and again in 1951 during her second pregnancy; since then there has been no recurrence. The children were normal. Patient is definitely light-sensitive. Clinically the eruption suggested disseminating subacute lupus erythematosus and was so diagnosed by several well-trained dermatologists, but three biopsies ruled out this diagnosis and confirmed the diagnosis of erythema annulare centrifugum. The patient has remained well to date (September, 1954).

A biopsy specimen (Fig. 3) from a 2-cm. lesion on the hip showed an epidermis which was slightly thicker than normal and a slight amount of intracellular edema. A few areas showed slight crusting. Just below the papillary layer, there was a discontinuous zone of monocytes, principally lymphocytes, and a similar light perivascular infiltrate throughout the rest of the cutis. Biopsy examination of a specimen from the left shoulder showed areas of slight atrophy of the epidermis with some intracellular edema of the basal layer resembling that seen in moderately acute lupus erythematosus. Throughout the epidermis there were small bands of perivascular lymphocytic infiltrate, most of which were not periappendageal. Although in this section the epidermal changes were suggestive of moderately acute lupus erythematosus, the deeper infiltrate was not compatible with this diagnosis.

Case 2.—Mr. A. I., aged 34, was first seen in February, 1949, complaining of an eruption of two weeks' duration. On his back there were two oval erythematous, slightly infiltrated edematous plaques. One was about 2 by 4 cm., and the other was about 5 cm. in diameter. The larger one showed central yellow clearing and a 2-cm. active, erythematous, infiltrated, nonscaly border. Biopsy specimen was taken from the border. The lesions were given 12 weekly roentgen ray treatments of 60 r each through 0.5 mm. of aluminum; after this the plaques involuted, but there was a tendency toward recurrence. During the treatment the patient also received, for a rheumatic condition, 2 gm. of chlortetracycline (Aureomycin) a day for two weeks, with essentially no change in the skin lesions. When he was seen in August, 1949, his eruption had disappeared, and when he was last seen in July, 1952, there had been no recurrence of his erythema annulare centrifugum.

Histologic examination (Fig. 4) showed a thin epidermis, but the pegs were still present. There was no edema of the epidermis. In the subpapillary layer and throughout the cutis there were well-defined areas (up to about 300 μ wide) of infiltrate consisting of small monocytes. The dense, predominately lymphocytic infiltrate was suggestive of an early lymphoma but was more characteristic of erythema annulare centrifugum.

COMMENT

In Case 1, the clinical picture and laboratory studies suggested disseminating subacute lupus erythematosus, but the histologic picture from three biopsies was compatible not with this diagnosis but with the histopathology of erythema annulare centrifugum. Case 2 showed a typical picture clinically and histologically of erythema annulare centrifugum. Butler's [8] histologic description ("Histologic examination showed an epidermis which was essentially normal with a slightly lamellar hyperkeratotic scaling. There was a rather marked lymphocytic infiltrate in the papillary and subpapillary portions of the cutis, which was arranged particularly along the horizontal blood vessels. The infiltrate was not specific in type, but did not contain plasma or giant cells") illustrates the histologic picture which we are presenting as diagnostic of erythema annulare centrifugum. We would substitute the words "that the infiltrate is characteristic or rather specific" for Butler's words "the infiltrate is not specific" for the histologic picture of erythema annulare centrifugum.

The important question on terminology is whether the noninfiltrated forms as described by Wende, Jillson and Hoekelman, Gammel, and others are the same disease as the infiltrated forms described by Darier and Butler. Our Case 1 is an example of the noninfiltrated type, while Case 2 is typical of the infiltrated form.

Our studies suggest that they show a similar histologic picture. In the infiltrated form, the histopathology is rather diagnostic, about as diagnostic as the histology of lupus erythematosus, secondary syphilis, and similar inflammatory diseases. From the clinical point of view, the evidence suggests that erythema annulare centrifugum, especially the superficial type, is a toxicodermatosis and may at times be an epidermophytid reaction. The presence of some scaling or even slight crusting at the inner edge of the active border is rather characteristic of erythema annulare centrifugum.

SUMMARY

After a review of the literature on the persistent annular erythemas usually called erythema annulare centrifugum, we concluded that this disease had been reported under a variety of names. Clinically, the picture may be fairly characteristic, showing annular plaques which migrate slowly; the lesions may show some scale or very superficial crusts at the active borders, and there is no definite predilection as to age and sex. The condition tends to be chronic and the response to therapy is variable, although roentgen ray treatment frequently gives good results. The clinical picture may be variable and may be a difficult diagnostic problem.

After a study of the histologic picture from 15 cases, we arrived at the conclusion that the histology of erythema annulare centrifugum is usually quite characteristic, showing an epidermis that is essentially normal or with variable evidence of edema and scale. In the cutis there is usually a mild subepidermal nonspecific infiltrate but in the mid and deeper cutis there are narrow zones of small mononuclears which are perivascular but usually not especially periappendageal. There is usually no nuclear debris.

CONCLUSIONS

Erythema annulare centrifugum is apparently a toxicodermatosis and the noninfiltrated forms have been reported as "id" reactions due to epidermophytosis, breast cancer, infections, and other diseases.

The histologic picture of erythema annulare centrifugum is usually diagnostic, especially if the lesions clinically are infiltrated. The histologic picture of the macular forms may be less diagnostic.

8. E. Madison St. (2).

ABSTRACT OF DISCUSSION

DR. CARL W. LAYMON, Minneapolis: The subject of the persistent, annular erythemas is difficult since these disorders are extremely uncommon and little is known concerning their cause. In a recent article in *Der Hautarzt*, Sonck discussed various etiologic theories (too numerous to mention), with special reference to the endocrines. He studied a woman with erythema annulare centrifugum whose lesions stopped progressing premenstrually, only to start enlarging at the onset of the menses. No definite conclusions were drawn.

In my opinion, many cases of chronic annular and gyrate urticaria, certain eruptions occurring in patients with carcinoma, atypical erythema multiforme, and dermatitis medicamentosa of the fixed type are diagnosed incorrectly as erythema annulare centrifugum.

Dr. Ellis stated the probability that erythema chronicum migrans differs from the other persistent, annular erythemas which he grouped with erythema annulare centrifugum. I agree with this view. Hellerstrom and others of the Scandinavian school have discussed erythema chronicum migrans of Afzelius and Lipschütz in detail. Apparently this is an extremely rare disorder in the United States, whereas in Scandinavia it is more frequent since Hellerstrom observed 30 cases in 13 years. All of the cases in Sweden followed the bite of a tick and some were complicated by meningitis and encephalitis. Whether or not the meningitis and other neurologic manifestations were due to an allergic-toxic reaction or to an infective agent has

not been settled, although a spirochete has been suggested as the causative organism because the patients recovered following the administration of bismuth, neoarsphenamine, oxophenarsine hydrochloride (Mapharsen), and penicillin, especially the latter.

Whether the other persistent, annular erythemas are variants of erythema annulare centrifugum should be regarded as questionable. An example is Gammel's case, termed "erythema gyratum repens," which occurred in a patient who had cancer in the breast. Dr. Ellis mentioned this case in his paper. The eruption involved the entire body except the hands and feet, and the configuration somewhat resembled the graining of a wooden panel ("cypress burl" was the term which was used). The lesions disappeared after the removal of the cancer and the axillary nodes.

There are many who agree with the view in Butler's article that only those eruptions should be classified as erythema annulare centrifugum which show a polycyclic or annular arrangement, keloidal consistency, and sudden disappearance of the lesions with subsequent recurrence.

Dr. Ellis concluded that the histologic picture of erythema annulare centrifugum is usually diagnostic, especially if the lesions are infiltrated. This might also be considered a debatable point. Recently I reviewed Butler's slides (and his case was certainly a characteristic one), but could not reach such a conclusion.

Dr. Ellis is to be commended for bringing a rare disease before the society and giving us the privilege of discussing the disorder.

DR. JOSEPH M. HITCH, Raleigh, N. C.: The chronic annular erythemas to me have always been a confusing hodgepodge. I used to think that if I read the descriptions often enough I would finally gain a precise conception of the fine distinctions between the various nosologic categories. However, such has not been the case, and when confronted with a disease suspected of belonging to this group I pull down the textbooks, carefully read the clinical descriptions, often with the lesion-bearing patient before me, and wind up by writing "erythema perstans group." It is, therefore, heartening to hear Dr. Ellis say that at least several of these so-called entities are indistinguishable even under microscopic scrutiny.

It seems to me the best course to follow in dealing with these cutaneous manifestations would be to group them all under a simple term such as "chronic annular erythema" and to place this material adjacent to that on erythema multiforme in the chapter on toxic erythemas. Then as specific causations are discovered such as the recent demonstration by Waisman (Waisman, M.: Trichophyton Rubrum Infection Simulating Erythema Perstans, *J. Invest. Derm.* **22**:287 [March] 1954) of Trichophyton rubrum in some of these lesions, the cases could be placed in their proper classification. In this connection I should like to ask Dr. Ellis if studies to rule out direct fungous infection were performed on his patients.

With the exception of specific local fungous infection, it would seem at this time that the preponderent evidence in regard to etiology of the whole group points to a circulating toxin or allergen. This concept has of course been promoted by many writers. Such toxins or allergens acting at either the dermal or the epidermal level, or both, assuming a configuration based on vascular arborization and dependent in regard to intensity on the fluctuating supply of the noxious substance could well account for the clinical variations.

Jillson and Hoekelman's (Jillson, O. F., and Hoekelman, R. H.: Further Amplification of the Concept of Dermatophytid, A. M. A. ARCH. DERMAT. & SYPH. **66**:738 [Dec.] 1952) demonstration that dermatophytids corresponding to the clinical morphology of erythema annulare centrifugum could be produced experimentally is strong support for the concept of a circulating noxious substance.

If this is true, then it is logical to assume that a bacterid may take the same form and remain present by virtue of support from a distant focus. If such a situation was intimated by Dr. Wise, Dr. McKee, and Dr. Traub in discussing the case presented by Dr. Gardner Hopkins (Hopkins, J. G.: Erythema Annulare Centrifugum [Squamous Form], A. M. A. ARCH. DERMAT. & SYPH. **40**:162 [July] 1939) at the New York Dermatological Society in 1939.

The same concept prevails in those cases of the Afzelius-Lipschütz variety which have been demonstrated to be due to insect bites and which were mentioned by Dr. Laymon.

In like manner it is not unreasonable to assume that a malignant neoplasm may at times produce a circulating substance capable of producing such eruptions. Dr. Gammel (Gammel, J. A.: Erythema Gyratum Migrans, A. M. A. ARCH. DERMAT. & SYPH. **66**:494 [Oct.] 1952)

presented such a case before this meeting in 1952, employing the term erythema gyratum repens. However, the following year, Stillians (Stillians, A.: Erythema Annulare Centrifugum, A. M. A. Arch. Dermat. & Syph. **67**:590 [June] 1953) reported a somewhat similar eruption associated with abdominal carcinomatosis, but he employed the term erythema annulare centrifugum.

Several reports of various internal diseases occurring concomitantly with persistent annular eruptions have appeared in the literature from time to time and are recorded in Stillians' recent article. Again it would not seem to carry us too far afield to postulate that such eruptions are reflections of noxious agents generated by diverse diseases.

Finally, I recall a recent case suggesting granuloma annulare or erythema annulare centrifugum. Histologically, the first diagnosis could be ruled out. Dr. Lever examined the slides and made a diagnosis of allergic vasculitis on the basis of vascular proliferation, thickening of the vessel walls, and inflammatory infiltrate, largely perivascular and including many eosinophiles. The biopsy was done early in the course of the disease. Perhaps later it would have reflected a picture more nearly like that described by Dr. Ellis.

When the concept is pursued that probably all of these chronic annular erythemas are of blood-borne "toxic" origin, the variations in the clinical picture offer little difficulty. Whether the lesion presents fine vesicles, scaling, or deeper cord-like infiltration would depend on the interaction of such factors as the nature of the toxin, its amount, sites, and abruptness of action, and the responsiveness of the tissues involved. For the same reasons, it would not be surprising to see considerable variation in the histologic picture. To have available histologic material from 15 cases of such a rare dermatosis is an unusual opportunity and is perhaps sufficient to form the basis of a definitive pathologic picture. However, I would be hesitant to accept such histologic findings as nonspecific monocytic perivascular infiltrate of the mid and deeper cutis coupled with negative features such as normality of epidermis, absence of periappendageal infiltrate and mild nonspecific infiltrate in the upper cutis as being diagnostic. I realize Dr. Ellis has specified that these findings are restricted to the infiltrated type of lesions, but this would certainly not make the other variants of erythema annulare centrifugum less bona fide members of the category.

I hope that Dr. Ellis will continue to collect and study histologic material from this group of dermatoses and especially specimens taken at various stages in the evolution of the lesions. If his original observations here are substantiated, it would indeed be a boone to clinical dermatology.

Dr. Jacob H. Swartz, Boston: I would like to ask Dr. Ellis whether he has noticed any association of Raynaud's disease with any of his cases of erythema annulare centrifugum. It could be just a coincidence, but in a few cases of the women that I have seen there has been present Raynaud's disease of varying degree. Perhaps the same noxious agent that is causing the erythema annulare centrifugum is found in Raynaud's disease.

Dr. J. Walter Wilson, Los Angeles: In Southern California at least we would have no trouble in assembling 15 or 20 cases which clinically would fit into this category, but in which the causative agent could be demonstrated to be Trichophyton rubrum.

I just want to warn against too small an effort to search for this organism as the cause. I believe it is advisable to implant rather large quantities of material taken from at least three different places on the borders of such lesions on to culture media—actually, this amounts to the implantation of superficial biopsy specimens. Too much reliance is often placed on a single culture or a single bit of material examined under the microscope.

Dr. Lawrence G. Beinhauer, Pittsburgh: After hearing this presentation, I would like to call your attention to an experience we had with a patient with skin manifestations which we classified as erythema annulare centrifugum. The patient, a woman, aged 28, had a persistent eruption of the body of 18 months' duration which resisted all therapy. After a complete study, a diagnosis of congenital hemolytic anemia was made. Following the removal of the spleen, the eruption spontaneously disappeared in four months. The pathological picture was similar to that presented by Dr. Ellis. We feel the eruption was definitely on a toxic basis and our experience was worthy of mention.

Dr. Stephen Rothman, Chicago: I noticed that Dr. Ellis has listed antihistaminics as noneffective. I had one patient with widespread erythema annulare centrifugum in which antihistaminics most satisfactorily controlled the eruption. This fits Thomas Lewis' contention that

peripherally spreading annular lesions are based on a histaminic mechanism. It seems that erythema annulare centrifugum belongs to the group of erythematous-urticarial toxic eruptions. Unfortunately, as in chronic urticaria, the eliciting toxic agent hardly ever can be found. I never succeeded finding it. However, the disease, although it may go on for years, is self-limited.

DR. FRANCIS A. ELLIS, Baltimore: This paper could have been simplified if we had included only the infiltrative forms of erythema annulare centrifugum, but for completeness we thought we should include also the macular forms.

I wish to repeat that I think that clinically and histologically, the picture is rather diagnostic in the infiltrated or papular forms. The macular types apparently can be caused my many different factors and in many cases may not be the same disease.

I thought that Butler's clinical and histologic description did fit the picture that we are presenting.

So far as antihistamines are concerned, I am certain that the antihistamines have been used in so few cases that we should not say they are of no value, but suggest that they be tried in more cases.

Fungous infections certainly were ruled out in the cases that I had personally and they should, of course, always be ruled out in all scaly macular lesions, especially if they are annular.

We did not see any associated Raynaud's disease. Many of our patients were fairly young and apparently had no vascular diseases. The patient with the infiltrated form reported in CASE 2 did have rheumatism.

How practical is the histologic diagnosis? Can we work the problem the other way? I think so, because looking over slides in the laboratory without knowing the clinical picture, histologic diagnosis has worked fairly well. Of course, histopathology is not going to be right all the time, any more than our other diagnostic aids.

One dermatologist said, "Ellis, you're all wrong. Look at this slide; you say that it is erythema annulare centrifugum, but the slide is from a patient who has a lymphoma." We checked back on the case and found that the man had had a "lymphoma" (?) for 10 years. Of course, he actually has had erythema annulare centrifugum for 10 years.

REFERENCES

1. Fox, T. C.: Erythema Gyratum Perstans, International Atlas of Rare Skin Diseases, London, J. & A. Churchill, Ltd., 1891, Pt. 5.

2. Wende, G. W.: Erythema Figuratum Perstans, J. A. M. A. **51**:1936, 1908.

3. Darier, J.: De l'érythème annulaire centrifuge, Ann. dermat. et syph. **6**:57-76, 1917.

4. Jadassohn, J.: Erythema Simplex Gyratum, in Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, Vol. 2, p. 656.

5. Strempel, R.: Erytheme mikrogyratum persistens, Dermat. Ztschr. **36**:63, 1922.

6. Lipschütz, B.: Über eine seltene Erythemform (Erythema chronicum migrans), Arch. Dermat. u. Syph. **118**:349, 1913.

7. Graham, T. N., and Throne, B.: Érythème Annulaire Centrifuge: Report of 6 Cases, Arch. Dermat. & Syph. **22**:777, 1930.

8. Butler, J.: Erythema Annulare Centrifugum, Arch. Dermat. & Syph. **25**:111, 1932.

9. Guichardot, M. P.: Deux cas d'érythème annulaire centrifuge, Bull. Soc. franç. dermat. et syph. **61**:583, 1951.

10. Gomez Orbaneja, J., and Vivancos, E.: Un caso de eritema anular centrifugo, Actas dermo-sif. **43**:446, 1952.

11. Gammel, John A.: Erythema Gyratum Repens: Skin Manifestations in Patients with Carcinoma of Breasts, A. M. A. Arch. Dermat. & Syph. **66**:494-505, 1952.

12. Jillson, O. F., and Hoekelman, R. A.: Further Amplification of the Concept of Dermatophytid, A. M. A. Arch. Dermat. & Syph. **66**:738, 1952. Jillson, O. F.: Allergic Confirmation That Some Cases of Annulare Centrifugum Are Dermatophytids, ibid. **70**:355, 1954.

13. Stillians, A.: Erythema Annulare Centrifugum: Its Relation to Internal Disease, A. M. A. Arch. Dermat. & Syph. **67**:590-593, 1953.

14. Klaber, R.: Erythema Gyratum Perstans (Colcott Fox): A Case Report, with Discussion on Relations with Erythema Centrifugum (Darier) and Dermatitis Herpetiformis, Brit. J. Dermat. **58**:111, 1946.

15. Lever, W.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

SUPPLEMENTAL BIBLIOGRAPHY

Fox, T. C.: Erythema Gyratum Perstans, in International Atlas of Rare Skin Diseases, London, J. & A. Churchill, Ltd., 1891, Pt. 5.

Lustgarten, S.: Erythema papulosum vel urticatum, figuratum, perstans et chronicum (Case Report), J. Cutan. Dis. **11**:110, 1893.

Arning, E.: Ein Fall von Erythema perstans pseudoleprosum, Arch. Dermat. u. Syph. **43**:11, 1898.

Sachs, O.: Erythema exsudativum perstans, Verhandl. deutsch. dermat. Gesellsch. **7**:405, 1901.

Donlos, G.: Érythème annulaire et diabète, Ann. dermat. et syph. **2**:431, 1901.

Finny, J. M.: Erythema marginatum perstans, M. Press & Circ. **75**:51, 1903.

Wende, G. W.: Erythema Perstans Involving Circinate Lesions, J. Cutan. Dis. **24**:241, 1906.

Block, B.: Érythème circiné récidivant (dermatitis herpetifmore, variété erythémateuse?) Ann. dermat. et syph. **8**:126, 1907.

Wende, G. W.: Erythema Figuratum Perstans, J. A. M. A. **51**:1936, 1908.

Lipschütz, B.: Über eine seltene Erythemform (Erythema chronicum migrans), Arch. Dermat. u. Syph. **118**:349, 1913.

Darier, J.: De l'érythème annulaire centrifuge, Ann. dermat. et syph. **6**:57-76, 1916-1917.

Jadassohn, J.: Erythema Simplex Gyratum, in Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, Vol. 2, p. 656.

Strempel, R.: Erytheme mikrogyratum persistens, Dermat. Ztschr. **36**:63, 1922.

Gammel, J. A.: Erythema Gyratum Repens: Skin Manifestations in Patients with Carcinoma of Breasts, A. M. A. Arch. Dermat. & Syph. **66**:494, 1952.

Clinical Notes, New Instruments and Techniques

S-FACTOR OF LIVER EXTRACT IN ACNE VULGARIS

JAMES W. BURKS Jr., M.D.
NEW ORLEANS
AND
JOHN M. KNOX, M.D.
OKLAHOMA CITY

Although the rationale for use of crude liver extract in the management of acne vulgaris has not been definitely established, many dermatologists consider it to be helpful. Sutton,[1] in 1928, first recommended liver in the form of a liver diet. Later Marshall * isolated from boiled liver extract a substance which proved to have therapeutic value for acne vulgaris; this he called S-factor or "skin factor." His work precipitated clinical studies by Lichenstein and Stillians [8] and by Boreen.[9] Although over half the patients in each series improved, the results were considered disappointing not only from the standpoint of effectiveness of treatment but also that of length of time required for improvement. These unenthusiastic reports apparently discouraged other investigators, for no further studies were published until 1948, when Walters [10] emphasized the value of crude liver and boiled liver extracts as supportive therapy. Nierman [11] noted definite improvement when S-factor was administered to 22 patients with cystic acne in whom routine therapy had failed. Among others who have observed the value of liver in the management of acne are Stokes and Sternberg,[12] Andrews, Domonkos, and Post,[13] and Mitchell-Heggs.[14] Whereas its value has been the subject of considerable controversy, no absolutely nullifying report has been found. In an attempt to confirm the presence of an acne-inhibiting substance in crude liver extract, we undertook a large-scale clinical evaluation of the S-factor.

MATERIALS AND METHODS

One hundred nineteen male patients and 31 female patients with acne at a large military installation † were treated with injections of S-factor ‡ and minimal supportive routine treatment. Of these 150, 11 were considered to have mild acne, 59 moderate, 52 moderately severe, and 28 extremely severe. S-factor was injected intramuscularly in doses varying from 1 to 2 cc. twice a week to 1 to 3 cc. daily, but most patients received 2 cc. three times a week, which was considered the optimal dosage. The supportive regimen employed consisted in (1) scrubbing the skin three times daily with a soapless detergent (pHisoderm) or sulfur soap; (2) shampooing the hair twice a week, as well as omitting the use of hair oil, and (3) eliminating from the diet a short list of foods rich in fat. In addition, acne surgery was performed when necessary, and topical and systemic administration of antibiotics was prescribed if pyoderma or folliculitis was present. No lotions, hormones, vitamins, vaccines, ultraviolet rays, cryotherapy, or roentgen rays were employed in these patients during this study.

Inspection of the data in the accompanying Table reveals that results were better in the group of patients receiving longer treatment. Improvement was observed in all grades of severity in approximately the same percentage of patients. The supportive regimen, although minimal, must be credited with at least a portion of the benefits observed. Nevertheless, results were superior to those that could be expected from supportive measures, psychologic factors, or spontaneous remissions. The evidence, therefore, would suggest an inhibitory effect of S-factor on the disease.

Assistant Professor of Clinical Medicine (Dermatology), Tulane University School of Medicine (Dr. Burks).

* References 2 to 7.

† United States Air Force Hospital, Keesler Air Force Base, Biloxi, Miss.

‡ S-factor (trade name, Kutapressin) was supplied by Kremers-Urban Co., Milwaukee.

Addition of S-Factor to Typical Therapeutic Regimen.—S-factor was added to a modern therapeutic regimen for acne in 76 private patients, in an attempt to determine if injections of this substance would decrease the time required for treatment, the over-all severity of the disease, or scarring. It readily became apparent that benefits derived from S-factor were too well concealed among results obtained from other measures to permit proper scientific evaluation of its effects. However, a study of these 76 patients yielded the following clinical impressions: (1) patients who receive S-factor improve slightly more than those who do not; (2) injections three times a week result in greater improvement than injections at weekly intervals; (3) cystic acne appears to be a good indication for use of the substance, and (4) acne indurata and acne of the hyperkeratotic follicular type do not respond well to this drug. Furthermore, injections of S-factor were less painful than those of crude liver extract and were accompanied by no untoward reactions in this study. Objective evaluation of any product used in treating acne, of course, must be made under controlled conditions, as in the first series of patients.

COMMENT

The mechanism for the therapeutic effect of liver on acne remains obscure. It has been attributed by various workers to the B vitamins, which decrease retention of tissue fluid,[15] to injection of a foreign material,[16] to correction of associated anemic states,§ and to the vasoconstricting action of the S-factor, with resultant decreased tissue edema and stasis.[7]

Results of Treatment of Acne Vulgaris by S-Factor in 150 Patients

	Response to Therapy *					
Duration of Treatment	0	+	++	+++	++++	Total
Under 3 mo.	6	9	22	26	7	80
Over 3 mo.	3	2	16	30	19	70
Total	9	11	48	56	26	150
	(6%)	(7.3%)	(32%)	(37.4%)	(17.3%)	

* 0 indicates unchanged by therapy; +, slight or questionable improvement; ++, definite, but not pronounced, improvement noted by patient and observers; +++, moderate inhibition of the disease with periodic new lesions, and ++++, pronounced inhibition of the disease with few or no new lesions.

CONCLUSIONS

Results in the present series of 226 patients corroborated previously published clinical reports that S-factor is a valuable adjunct in treatment of acne vulgaris. Further investigation is required to establish definitely the presence of an acne-inhibiting substance in crude liver extract. The potentialities of such studies are great, since S-factor has apparently never been isolated in pure form nor has it been chemically identified. Massive doses of this substance conceivably could be extremely effective in this disease.

§ References 17 and 18.

REFERENCES

1. Sutton, R. L.: Liver Diet in Acne Vulgaris and in Furunculosis, Arch. Dermat. & Syph. **18**:887-890 (Dec.) 1928.

2. Marshall, W.: Probable "S" Factor in Treatment of Acne Vulgaris with Liver Extract (Injected Subcutaneously), Med. World **57**:101-103 (Feb.) 1939.

3. Marshall, W.: Further Studies on Therapy of Acne Vulgaris with Modified Liver Extract, J. Invest. Dermat. **2**:205-218 (Aug.) 1939.

4. Marshall, W.: Simple Methods for Studying Skin Factors in Liver Extract: Clinical Observations on Cases of Acne Vulgaris, Northwest Med. **38**:467-469 (Dec.) 1939.

5. Marshall, W.: Subcutaneous Liver Extract Therapy for Acne Vulgaris: Studies with Distillation and Evaporation, Journal-Lancet **60**:117-120 (March) 1940.

6. Marshall, W.: Evaluation of Recent Data on Boiled Liver Extract Method of Treating Acne Vulgaris, Minnesota Med. **25**:796-797 (Oct.) 1942.

7. Marshall, W.: Liver Extract in Acne Eruptions, Abscesses and Scars: Therapeutic Role of Experimental Fractions, J. M. A. Alabama **13**:255-265 (Feb.) 1944.

8. Lichenstein, M. R., and Stillians, A. W.: Liver Extract in the Treatment of Acne Vulgaris in Tuberculosis Patients, Arch. Dermat. & Syph. **45**:959-962 (May) 1942.

9. Boreen, C. A.: Boiled Liver Extract in Treatment of Acne Vulgaris, Minnesota Med. **25**:276 (April) 1942.

10. Walters, J. D.: Collateral Findings and Supportive Therapy in Acne Vulgaris, Ohio M. J. **94**:697-699 (July) 1948.

11. Nierman, M. M.: Treatment of Cystic Acne Vulgaris with a Cutaneous Vasoconstrictor (Kutapressin), J. Indiana M. A. **45**:497-502 (June) 1952.

12. Stokes, J. H., and Sternberg, T. H.: A Factor Analysis of the Acne Complex with Therapeutic Comment, Arch. Dermat. & Syph. **40**:345-367 (Sept.) 1939.

13. Andrews, G. C.; Domonkos, A. N., and Post, C. F.: Treatment of Acne Vulgaris, J. A. M. A. **146**:1107-1113 (July 21) 1951.

14. Mitchell-Heggs, G. B.: Seborrheic Dermatitis and Acne Vulgaris, Brit. M. J. **2**:1079-1082 (Nov. 3) 1951.

15. Burgess, J. F.: Treatment of Acne Vulgaris, Canad. M. A. J. **62**:48-51 (Jan.) 1950.

16. Baird, K. A.: Results in Acne Vulgaris When Causal Factors are Treated Synchronously, Clinics **5**:754-762 (Oct.) 1946.

17. Pels, I. R.: Acne: A Review with Particular Reference to the Etiology and Treatment, Internat. Clin. **4**:255-288 (Dec.) 1936.

18. Symposium on the Practical Management of Acne Vulgaris (Various Authors), J. Invest. Dermat. **3**:143-157 (April) 1940.

UNUSUAL REACTION TO APPLICATION OF PODOPHYLLUM RESIN

THOMAS B. MAXWELL, M.D.
AND
JOHN H. LAMB, M.D.
OKLAHOMA CITY

The action of podophyllum resin (podophyllin) on the skin and on skin lesions such as warts and keratoses is well known and has been reported by many authors. This action is essentially a spasm of the small vessels resulting in ischemia, necrosis, and sloughing, with degeneration and the production of bizarre forms of epithelial cells.[1]

We wish to report two instances in which the reaction to podophyllin was most unusual.

REPORT OF CASES

CASE 1.—Mrs. B. R., a patient at Oklahoma University Hospital skin clinics for many years, had multiple skin cancers and keratoses. On Aug. 5 she called attention to a lesion on the right preauricular area which she stated had been treated with radium some 15 years previously for a skin cancer. There was a depressed, smooth, telangiectic scar which was bordered by a scaling erythematous process along the upper and outer edges. This process was believed to be a precancerous keratosis, and podophyllin (20% in tincture of benzoin) was applied weekly for five times. When the patient was seen after the last of these applications, there had been considerable extension of the process with thickening and infiltration of the edges to a much greater degree than originally. The examiners felt that this development possibly represented a squamous

Department of Dermatology, University of Oklahoma School of Medicine and State University Hospitals (Dr. Maxwell).

cell carcinoma. Since this rapid growth of the lesion had occurred in such a brief space of time, it was decided to delay definitive treatment and observe the lesion further. Cool boric acid soaks and a bland ointment were prescribed.

On her return in two weeks all reaction was gone and the edges of the scar were smooth and without evidence of keratosis or malignant growth.

Case 2.—Mr. R. E., aged 50, was examined on Aug. 19 in our office with a typical basal cell epithelioma, 1.5 cm. in diameter, located on the neck below the chin. This area, 25 years ago in Chicago, had received x-ray therapy for acne. There was deep scarring from acne with some telangiectasis, but the sebaceous glands were still active. Podophyllin is especially active in epithelioma arising in areas of the skin which have previously had a heavy dose of x-rays. From Aug. 19 until Oct. 5, podophyllin 20% in tincture of benzoin was applied at about weekly intervals. After the fourth application progress was satisfactory, and the lesion was much smaller. On examination shortly after the sixth treatment, it appeared that there had been considerable spread of the epithelioma. The lesion was about twice the size as originally. The edges were rolled and indurated; there was crusting and a little ulceration centrally. A small piece of skin was removed from one edge for biopsy.

The biopsy report was as follows:

Examination of the tissue showed an extremely thick hyperkeratosis and parakeratosis of the epithelium. The epithelium was well preserved for the most part and had a distinct granular cell layer; there was acanthosis manifested both by widening of the rete malpighii and lengthening of the rete pegs. There were a few mitotic figures, and many cells showed intercellular edema. Scattered through the thickened stratum corneum were many polymorphonuclear leucocytes. In the corium was an inflammatory infiltrate composed of lymphocytes and neutrophiles. There was no evidence of malignancy in the section.

Impression was pseudoepitheliomatous hyperplasia.

On conservative therapy the reaction subsided until, after three weeks, there was little residual of either the original lesion or the reaction following the use of the podophyllin.

SUMMARY AND COMMENT

A hyperplastic, infiltrated reaction to the application of podophyllin simulating epithelioma in two patients is described. Biopsy in one of these showed only pseudoepitheliomatous hyperplasia. This reaction is the antithesis of what one expects from local application of podophyllin. Bland treatment and time are to be preferred to immediate radiation or surgical intervention.

The mechanism is not known; possibly it is an allergic response.

Podophyllin is a known sensitizer in addition to being a primary irritant.

REFERENCE

1. Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata and Verrucae Vulgaris, Arch. Derm. & Syph. **56**:30-45 (July) 1947.

DERMATITIS DUE TO BLACK WALNUT JUICE

JOHN M. SIEGEL, M.D.
ALLENTOWN, PA.

A search of the literature reveals no report of contact dermatitis due to walnut juice; this, in spite of the fact that large numbers of people contact black walnut hulls during the walnut picking season, and the juice of black walnuts has been used for centuries for covering depigmented areas of vitiligo and scars. The Depelle Company of San Francisco,* one of the few remaining pharmaceutical houses manufacturing walnut juice for medical purposes, reported no sensitizing or irritating properties from their brand of natural walnut juice. Schwartz [1] reported

From the Dermatology Division, Medical Service, Sacred Heart Hospital.

* Personal communication to the author.

five cases of contact dermatitis due to walnut wood, but the condition occurred in workmen in a cabinet-making plant handling Brazilian walnut wood. Schwartz † stated he never saw any irritation due to the juice of the ordinary black walnut (Juglans nigra).

For these reasons, it was felt the following case was worthy of reporting.

REPORT OF A CASE

H. B., a white man, aged 44, was seen in the outpatient department of the Sacred Heart Hospital on Oct. 6, 1952, with the complaint of a burning, itching, blistering eruption in all the finger webs. For two days prior to his visit to the hospital, he had been "picking black walnuts," his first experience at this work. He did not employ any protective measures, nor was he careful to wash his hands.

Examination revealed a healthy, middle-aged, bedraggled appearing white man of obviously low intelligence. His clothes and all exposed parts of his body were splattered with a brownish stain. His hands, particularly the fingers and finger webs, were especially noteworthy. Here, there was a heavy, blackish-brown stain, and in all the interdigital spaces and webs were large flaccid bullae and blebs, some 1 to 2 cm. in diameter.

Bullae in finger webs and interdigital spaces, after picking black walnuts.

The diagnosis of acute contact dermatitis due to walnut juice was made. Treatment with cool, weak aluminum acetate (Burow's solution) compresses and boric acid ointment was instituted. Approximately 10 days later, the eruption was entirely clear.

About one month later, in an effort to reproduce the eruption under controlled conditions, the patient was asked to shell approximately 10 lb. (4.5 kg.) of black walnuts. Aside from the brownish-yellow stain which remained on his hands for about two weeks, no untoward reaction occurred.

COMMENT

The absence of dermatitis on the other exposed parts of the body and hands which were also heavily stained with the walnut juice, together with the negative reexposure test to walnut hulls, points towards a primary irritant effect of the walnut juice as the cause, rather than an allergic sensitivity.

The walnut juice collected in pools in the webs and intertriginous areas of the fingers which combined with the macerating effect of the moisture itself over a number of hours produced the enormous bullae described.

† Schwartz, L.: Personal communication to the author.

COMMENTS ON TECHNIQUE OF ACNE PLANING

It is interesting to note that in the 21st edition of the Dispensatory of the United States of America,[2] published in 1926 (no mention is made of the substance in two later editions), Juglans, or black walnut hull extract, is recommended as a laxative, a vermifuge, and a bitter. A volatilizable acid—julandic acid—is present in the crude walnut hull extract. This substance is related chemically to chrysophanic acid, an irritant well known for its astringent properties.

SUMMARY

A hitherto unreported cause for contact dermatitis is described—black walnut juice. It can act as a primary irritant in walnut pickers who employ no protective or sanitary measures. The specific irritant is probably julandic acid, an astringent related to chrysophanic acid.

REFERENCES

1. Schwartz, L.: Dermatitis Venenata Due to Contact with Brazilian Walnut Wood, Pub. Health Rep. **46**:1938-1942 (Aug. 14) 1931.

2. The Dispensatory of the United States of America, Ed. 21, Philadelphia, J. B. Lippincott Company, 1926, pp. 600-601.

COMMENTS ON THE TECHNIQUE OF ACNE PLANING

LIEUTENANT COMMANDER W. R. HUBLER (MC), U.S.N.R.

The rotating wire brush treatment for acne scars recently reported [1] has been of value in my experience. However, freezing of the skin with the ethyl chloride spray obscures the scars, making it difficult to locate the exact areas to be treated.

A technical improvement which I have found helpful is the use of 1% methylrosaniline chloride N. F. (gentian violet) to delineate the scarred areas. At first it was used only to outline the desired areas, but further experience has shown the advantage of painting the entire area to be treated. Not only does the methylrosaniline chloride delineate the area to be treated, but the rotating wire brush removes the dye with each stroke, showing the exact area which has been treated. This is very advantageous, because the frozen skin does not bleed and it is difficult to determine the effective width of each stroke of the brush or the site treated with the preceding stroke.

The depth of treatment can also be judged by the completeness of the removal of the methylrosaniline chloride. Since methylrosaniline chloride is a mild bactericide, it also serves to reduce the skin bacterial count preoperatively.

The use of rubber gloves on the left hands of the operator and assistant is helpful in protecting the fingers from the cold while holding gauze to confine the ethyl chloride spray during the freezing process.

Prior to the use of the methylrosaniline chloride technique, it was necessary for us to repeat the "plastic planing" four to six times. Since then we have achieved as good results with two treatments.

We have had no postoperative infections. Bismuth tribromphenate (Xeroform) gauze and pressure dressings are applied for 24 hours. These are then soaked off, and no further dressings are applied. A thin layer of antibiotic ointment is used three times daily until the skin has healed.

The opinions are those of the author and do not reflect the opinion of the Navy service at large.

REFERENCE

1. Kurtin, A.: Corrective Surgical Planing of Skin: New Technique for Treatment of Acne Scars and Other Skin Defects, A. M. A. Arch. Dermat. & Syph. **68**:389-397 (Oct.) 1953.

STREPTOMYCIN AND ISONIAZID IN TREATMENT OF ERYTHEMA INDURATUM (BAZIN'S DISEASE)

T. PASIECZNY, M.D.
GLASGOW

Erythema induratum is a chronic recurring disorder, usually involving the skin of the legs of young women, characterized by deeply situated nodosities and ulcerations. Patients suffering from erythema induratum often have a poor peripheral circulation, as evidenced by cold, blue hands, or a chilblain tendency.

Investigations carried out by various dermatologists at the beginning of the century established the tuberculous nature of this condition.

According to recent Medical Research Council publications, good results have been obtained in other tuberculous infections by means of streptomycin and isoniazid (isonicotinic acid hydrazide). It was decided to treat several cases of erythema induratum in this way.

METHOD OF TREATMENT

One gram of streptomycin was given daily for 30 days (except Sundays) by intramuscular injections, and on the same days 100 mg. of isoniazid was given morning and evening by mouth.

REPORT OF CASES

Ten cases of erythema induratum—all women between the ages of 19 and 53 years—were treated with streptomycin and isoniazid. These cases were selected from a larger group, which may be clinically similar, e. g., erythema nodosum and nodular vasculitis, and the duration varied from six months to nine years. The distribution of the lesions was typical in six cases; in three, there was a wider distribution, involving the thighs and buttocks also. In one case only one leg was involved. Full-scale physical examinations and blood investigations revealed no abnormalities. The biopsy in each case showed the typical histological appearances associated with erythema induratum. All patients were treated as outpatients. All cases had been treated previously with various ointments, ultraviolet lamp therapy, and a vitamin K preparation (Tablets Synkavit), and one patient with penicillin injections and paraaminosalicylic acid (PAS).

RESULTS

From the 10 cases treated an excellent inital response was obtained in 9 cases and a moderate improvement in 1 case. By the end of the second week or by the beginning of the third week of treatment, the skin lesions of all the patients were subsiding rapidly, and the pain had disappeared. The patients complained only of some mild general weakness and slight headaches. No serious side-effects were observed. All stated that their appetite was increasing. All of them put on weight—one patient 13½ lb. (6 kg.). At the end of treatment, the nine good cases showed only some discoloration of the skin with scarring.

Case 5 in the series was only moderately improved, and six weeks after treatment a few fresh nodules and ulcers appeared on both legs. Of the nine successfully healed cases one case remained well for three and a half months, but after that time scattered painful nodules appeared again on both legs. Case 6 improved dramatically during the third week of the treatment, leaving only fine scars on the completion of the treatment. After four months, a few fresh nodules appeared twice at two-week intervals, but these healed spontaneously and still remain healed. At the time of the relapse the patient was under treatment for rheumatoid arthritis with phenylbutazone (Butazolidin). Observation of cases was continued from four to nine months.

One case, which is not included in the series, was a woman, aged 21, who had suffered from rather severe erythema induratum for over one year. After the first injection of streptomycin she developed, one hour later, a very severe urticaria. Treatment was stopped and antihistamines were given. Four days later, when the urticaria had subsided completely, 0.5 gm. of streptomycin was given, but again a severe urticaria appeared. Four days later, isoniazid was given

Dermatological Department, Glasgow Royal Infirmary.

alone, and in three weeks all the ulcers and nodules had disappeared. The treatment was continued for six weeks. The result still remains very good after six months' observation. To avoid drug resistance, this experiment was not repeated in other cases.

SUMMARY

Ten patients suffering from erythema induratum were treated with streptomycin and isoniazid (seven cases, very good; one case, good; two cases, bad). Results after nine months' observation are encouraging. A further report will follow.

Permission for the publication of this article was given by Dr. Harvey.

REFERENCES

1. Streptomycin and Isoniazid: Second Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Brit. M. J. **1**:521 (March) 1953.

2. Isoniazid in the Treatment of Pulmonary Tuberculosis: Third Report to the Medical Research Council by Their Tuberculosis Therapy Trials Committee, Brit. M. J. **1**:630 (March) 1953.

3. Adoni, L.: Streptomycin in the Treatment of Cutaneous Tuberculosis, A. M. A. Arch. Dermat. & Syph. **68**:363 (Oct.) 1953.

4. Leider, M., and Sawicky, H.: Assay VIII: Isonicotinylhydrazine Rimiform (R) in the Treatment of Tuberculosis Cutis, J. Invest. Dermat. **21**:49 (July) 1953.

5. Isoniazid in Combination with Streptomycin or with PAS in the Treatment of Pulmonary Tuberculosis: Fifth Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Brit. M. J. **2**:1005 (Nov.) 1953.

HEPARIN IN TREATMENT OF PSORIASIS

PAUL LeVAN, M.D.
LOS ANGELES

A recent article appearing in the ARCHIVES, July, 1953, reports the use of heparin in the treatment of psoriasis.[1] This preliminary report sets forth the clinical results obtained in three patients with psoriasis treated with heparin. The author believes that heparin may prove of value in the treatment of psoriasis and urges further clinical trial of this drug. No controls were used in the reported study.

Approximately 18 months ago an investigation of the use of heparin in the treatment of psoriasis was undertaken at the Veterans Administration Hospital at Los Angeles. The rationale for the use of heparin in psoriatic patients was based upon the report of Grütz and Bürger,[2] who found an increase of total fats in the serum of psoriatic patients. Heparin has been found to reduce the amount of the large molecule lipoid fractions, as measured by the Goffman [3] technique, in the serum of atherosclerotic patients. It was felt that a change in the relative amounts of large- and small-moleculed lipoid fractions might influence the lesions of psoriasis.

The first six patients treated with 100 mg. of heparin intravenously, five days each week, showed a rapid response to this therapy. In most instances, the acuteness and severity of the process diminished in two to three weeks, although all of these patients still presented some residual psoriatic lesions. Controls were then initiated by the use of 1 cc. of isotonic sodium chloride solution injected intravenously, for five days of each week, into patients with psoriasis. The patients were not told which of the two substances they were receiving. In a series of six

From the Division of Dermatology, Department of Medicine, University of California at Los Angeles, and the Wadsworth General Hospital, Veterans Administration Center.

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control patients, who were on the same hospital regimen as the initial heparin-treated group, a similar response of the psoriatic lesions was observed. These patients improved greatly in a matter of two to three weeks while confined to the hospital.

In a group of five additional patients treated with heparin, subsequent to the initial group, little or no response to therapy was observed. Two patients who had responded rather dramatically to heparin treatment initially were re-treated after having experienced clinical relapse without any effect. One of these patients subsequently improved while on the saline control regimen. In all, 12 patients were treated, 7 of whom showed improvement and 5 of whom failed to improve. Six control subjects receiving isotonic sodium chloride solution showed clinical improvement, while two showed no improvement.

From the foregoing, it is our conclusion that heparin has no specific effect in the treatment of psoriasis. The improvement noted in both the heparin-treated and control groups may be attributed to the psychological effect of receiving injections and the benefits of hospitalization.

It would seem that this information should be made available to avoid the widespread use of heparin in the treatment of psoriasis.

6317 Wilshire Blvd. (48).

REFERENCES

1. Jekel, L. G.: Use of Heparin in Treatment of Psoriasis, A. M. A. Arch. Dermat. & Syph. **68**:80-82 (July) 1953.

2. Grütz, O., and Bürger, M.: Die Psoriasis als Stoffwechsel Problem, Klin. Wchnschr. **12**:373-379 (March 11) 1933.

3. Graham, D. M., and others: Blood Lipids in Human Atherosclerosis: Influence of Heparin on Lipo-Protein Metabolism, Circulation **4**:666-673 (Nov.) 1951.

SCAR IMPRINTS AND MOLDS

DAVID C. FRISCH, M.D.
PORTLAND, ORE.

Sandpaper surgery has produced cosmetic improvement for facial scars. The record of such improvement has usually been preserved with photographs. A better record may be obtained with impression molds like those used in dentistry. The technique to be described is satisfactory but there is still much room for improvement. Other methods are still being investigated, such as positive vs. negative molds and plaster vs. rubber or agar molds.

Imprinting on flat surfaces similar to the fingerprint technique was unsatisfactory. Of this type, Scotch tape applied to stained skin was the best. The total number of scars could be recorded but not the depth of the scars. Other unsatisfactory methods using monochrome latex rubber in multiple layers were tried. In these there was little contrast and not enough support for permanent storage, and the process was time consuming. A latex rubber mold using two different colors was unsatisfactory because it was very difficult to fill the scars alone without staining the surrounding normal skin.

So far the most satisfactory mold has been a contrast type. It shows pores, is easily accomplished, and can be folded and stored with the patient's chart. One rubs a liquid black foundation lotion into the scars and normal skin. Mine is made by adding charcoal to Ar-Ex foundation lotion. Additional dilution with water is made to compensate for increased powder content. This lotion rapidly dries on the face. When Scotch tape is repeatedly applied to the skin, most of the stain is removed from the normal skin, but the scars retain the pigment. When the painted face is ready for the latex, the scars show up strongly, and photographs can be taken at this time for a more accurate record. Two coats of pure white rubber latex are then applied (Plastico No. 10). Deep scars may require additional applications to fill the cavity. Scars to be excised may be painted with a thicker red rubber latex, differentiating these from those to be sanded. The white latex becomes transparent when dry and is then ready for the backing. Adhesive tape strips are applied carefully over the latex, covering the area like a mask. When the mask is removed, the

Fig. 1.—Showing the darkened face. Observe the stained scars and dilated pores.

Fig. 2.—Wet latex has been applied to the blackened face.

Fig. 3.—The adhesive tape backing has been applied to complete the mask.

latex peels off the face. The edges of the mask are immediately trimmed to prevent the exposed raw tape surfaces from folding over on to the mold. The latex-covered tape surfaces will not adhere. The masks are labeled, folded into envelopes and stored with the patient's record.

Several records of scars before and after surgery have now been obtained. Visually one can see improvement on the mask, and can feel the differences in depth of the remaining scars. The scars are stained black in contrast to the white of normal skin and are sharply outlined. One may see a scar on a postoperative mask apparently the same size as before. However, comparisons made by running one's finger over the masks reveal great decrease in depth. The patient, because of the decreased shadow produced by the scars, has a marked clinical improvement. The masks do show a marked decrease in the number of dilated pores and the complete eradication of small or moderate-sized scars.

329 Mayer Building (5).

HYPERLIPEMIC XANTHOMATOSIS IN A PATIENT WITH SUBACUTE GLOMERULONEPHRITIS (NEPHROTIC STAGE)

WILLIAM B. TAYLOR, M.D.
AND
ARTHUR C. CURTIS, M.D.
ANN ARBOR, MICH.

Thannhauser has divided the xanthomatoses associated with altered blood lipids into two main groups: (1) hypercholesteremic xanthomatoses and (2) hyperlipemic xanthomatoses. In the first group, the fasting blood serum is clear; in the second group the serum is milky or chylous.

The entities described in the hyperlipemic group (2) are the following:

A. Idiopathic hyperlipemia with secondary xanthoma
   1. Idiopathic (familial) hyperlipemia in children with hepatosplenomegaly and secondary xanthoma
   2. Idiopathic hyperlipemia in adults with secondary xanthomas occasionally accompanied by glycosuria and hepatosplenomegaly

B. Syptomatic hyperlipemia with secondary eruptive xanthoma
   1. Xanthoma diabeticorum
   2. Hyperlipemia in chronic pancreatitis and eruptive xanthoma
   3. Hyperlipemia in glycogen storage disease (von Gierke's disease) and eruptive xanthoma
   4. Hyperlipemia in lipid nephrosis

It has been pointed out by Thannhauser that xanthomatosis has never been reported in association with the hyperlipemia of lipid nephrosis or the nephrotic stage of glomerulonephritis. A recent search through the literature has likewise been devoid of any such reports. For this reason we feel it worth while to present the following report as an example of secondary eruptive xanthoma occurring in a patient with subacute glomerulonephritis in the nephrotic stage.

REPORT OF CASE

J. W., #616062, a 17-year-old white girl, entered the University Hospital on June 3, 1947, with the chief complaint of weakness and swelling of the legs.

She had been in good health until late December, 1946, when a severe upper respiratory infection occurred, lasting 10 days and unaccompanied by a sore throat.

From the Department of Dermatology and Syphilology, University of Michigan Hospital, University of Michigan School of Medicine.

On Feb. 3, 1947, while playing basketball, she became aware of weakness and shortness of breath. Seven days later, swelling of the lower abdomen and legs, severe headaches, nausea and vomiting, and blurring of vision occurred. At that time her family physician told her that her urine contained albumin (4 +) but no blood.

She was hospitalized in Ohio for three weeks beginning Feb. 19, 1947, on a low-salt, high-protein diet; plasma was administered along with oral and intravenous diuretics. The edema disappeared while the patient was in the hospital but gradually returned after discharge and she became progressively worse. In May, 1947, three small yellowish nodules on the left elbow and two on the right elbow were observed.

The rest of the history was not significant.

The patient was admitted to the University Hospital on June 3, 1947, with a pulse rate of 110 per minute, blood pressure 140/105, temperature 97 F., height 5 ft. 4 in. (163 cm.) and weight of 121 lb. (54.9 kg.) (normal weight 112 lb. [50.8 kg.]).

She had a severe generalized edema. The eyelids were slightly edematous. Pitting could be demonstrated on the legs, thighs, sacrum, hands, and arms. The pupils of her eyes were equal and round, and reacted to light and in accommodation. The visible structures in the ocular fundi were slightly hazy, but no hemorrhages were seen. The nose and mouth were

Laboratory Findings

Date	Total Serum Cholesterol, Mg. per 100 Cc.	Serum Proteins				Urine Albumin	Non-protein Nitrogen	Edema	Xanthomas	RBC in Urine
		Alb.	Glob.	Total Protein	A. G. Ratio					
6/ 3/47	900	...	...	...	....	++++	44.8	severe	present	20-25
6/11/47	...	...	...	...	....	+++	....	severe	present	3-4
6/17/47	...	1.6	2.9	4.5	0.55	+++	34.1	.....	present	3-4
6/19/47	...	...	...	...	....	++++	....	none	present	2-3
6/24/47	910	...	...	...	....	++	....	.....	present	3-4
7/ 2/47	1,170	1.9	3.2	5.1	0.69	+++	....	none	present	8-10
7/10/47	858	2.4	2.9	5.3	0.83	++	....	none	present	6-8
8/ 6/47	...	1.6	3.1	4.7	0.51	.....	....	.....	.....	...
8/26/47	488	2.5	2.8	5.3	0.90	++	37	none	none	0
9/24/47	317	2.7	3.0	5.7	0.90	++++	....	.....	none	Occ.
4/ 9/48	286	3.3	2.4	5.7	0.14	+++	28	none	none	1-3
12/ 3/48 *	332	3.1	2.9	6.0	1.1	+++	43	none	none	1-2

* Blood pressure 124/86. Urinary concentration test showed a maximum concentration of 1.019 corrected for 1% protein. Blood urea nitrogen 16.4%; serum sodium 144 mEq. per liter; serum creatinine 1.02 mg. per 100 cc.

normal. There was slight injection of the fauces and pharynx. The bases of both lungs were flat to percussion and fremitus was present. The heart was not enlarged. The aortic second sound was accentuated. There were no murmurs. Examination of the back was normal; there was no tenderness of the spine or costovertebral tenderness. A 4 + sacral edema was present. The abdomen was tense and distended. No organs nor masses were palpable. There was no edema of the abdominal wall. The pelvic and rectal examinations were normal. There was slight cervical adenopathy. The tendon reflexes were normal. In the skin over the right elbow there were three orange-yellow papules 4 mm. in diameter and two similar lesions on the left elbow.

The serum of blood drawn for laboratory studies was milky. The Kahn test for syphilis was negative. The basal metabolic rate was — 20. The fasting blood sugar was 73 mg. per 100 cc. The two-hour urea clearance test averaged 53% excretion.

On June 3, 1947, the total serum cholesterol was 900 mg. per 100 cc. Examination of the urine showed a 4 + reaction for albumin; microscopically there were 20 to 25 red blood cells per high-power field and many hyaline casts. On June 17, 1947, the total serum protein was 4.5 gm. per 100 cc. (albumin 1.6 gm. and globulin 2.9 gm.); albumin-globulin ratio 0.55), urine albumin 3 +, 3 to 4 RBC per high-power field, and nonprotein nitrogen 34.1 mg. Other significant laboratory data during and after this admission are presented in the table.

The diagnosis of subacute glomerulonephritis in the nephrotic stage and xanthomatosis was made. Several members of the dermatology staff concurred in the latter diagnosis. The patient

was given a 350 mg. salt, 40 mg. protein, 2,500 calory diet, ammonium chloride 3 gm. t.i.d., three days on, three days off, dibasic calcium phosphate 1 gm., t.i.d. and bed rest. Her condition improved, and she was discharged July 10, 1947, with the advice to continue the diet and bed rest at home. The xanthomas were still present at that time, but on Aug. 26, 1947, when she returned to the hospital they had disappeared. On this date her total serum cholesterol had fallen to 488 mg. per 100 cc. She remained well clinically, although laboratory studies revealed residual kidney damage (Table). She was last seen on Dec. 3, 1948.

COMMENT

It is unfortunate that more complete lipid studies were not done on this patient and that the xanthomas were not proved pathologically. However, we believe this patient had eruptive xanthomas due to the hyperlipemia of the nephrotic syndrome and subacute glomerulonephritis, because the skin lesions appeared at a time when the nephrosis was most severe and the blood cholesterol was high. Since the total cholesterol was 900 mg. per 100 cc. and the serum "milky" the neutral fat was extremely high. With a milky serum the hypercholesteremic group of xanthomas can be eliminated because in the latter the serum is clear. The individual skin lesions were diagnosed as xanthomas by several dermatologists. The skin lesions persisted while the hypercholesteremia and hyperlipemia were present and disappeared when the cholesterol fell to 488 mg. per 100 cc. and below.

If the xanthomas had disappeared on a low-fat diet, it would be difficult to rule out idiopathic hyperlipemic xanthomatosis complicating the nephrosis. However, this was not the case because the patient's diet contained about 150 mg. of fat per day. In addition, the hyperlipemia and hypercholesteremia continued to improve with the clinical improvement of the nephrotic syndrome.

SUMMARY

The case summary of a patient whom we believe had secondary eruptive xanthomas due to the hyperlipemia of the nephrotic stage of subacute glomerulonephritis is presented. To our knowledge this association has never before been reported.

REPEATED "FREEZE-THAW" AS A CRYOTHERAPEUTIC TECHNIQUE

ABNER KURTIN, M.D.
AND
NORMAN ORENTREICH, M.D.
NEW YORK

In an article recently published[1] ethyl chloride was used as a refrigerating agent. In the early work it was noted that an unexpectedly severe local reaction followed if an area was refrozen soon after it had thawed. Experiments were performed to explain this observation. It was shown that ethyl chloride refrigeration continuously maintained for a specific time period produced much less reaction than if repeated freezing, thawing, and refreezing were performed in the same time period.

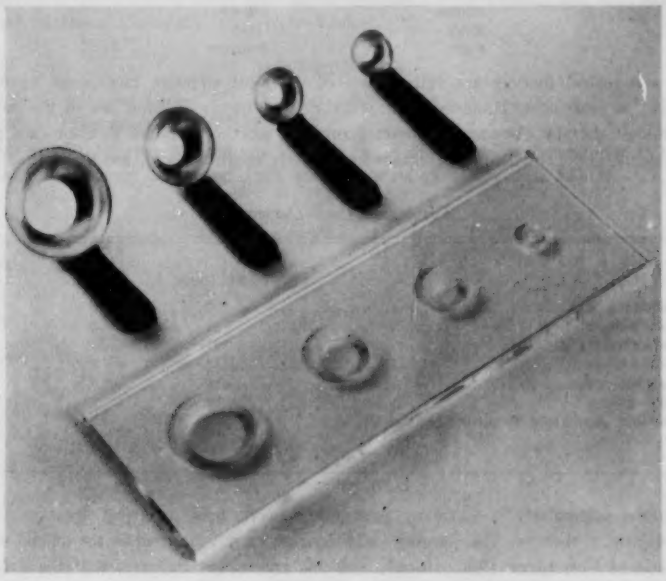
This clinical procedure is analogous to the laboratory disruption of cell walls by repeated freeze-thawing which is used as a standard biochemical technique in the study of protoplasm. The phenomenon may also be noted in the home when frozen foods which have been thawed and refrozen become unpalatable because of the destruction which occurs. Cellular disruption is consequent to crystal formation and expansion of frozen protoplasm. Repeating the process will increase the extent of disruption.

We have shown "freeze-thaw" to be of therapeutic value in certain acanthotic and hyperkeratotic dermatoses in which controlled cryotherapy is indicated. The following dermatoses have responded well to this local treatment: recalcitrant plaques of psoriasis, hypertrophic lichen planus, lichen simplex, and inveterate thickened plaques of atopic dermatitis. Similar "freeze-thaw" results have been obtained with solid carbon dioxide and liquid nitrogen in the treatment of plantar warts and cavernous angiomas.

PROCEDURE

Freezing with ethyl chloride spray is aided by a continuous blast of cold air. The temperature attained is —30 C. as measured by toluol thermometer. The thawing cycle is hastened by a hot air blast. A small hair dryer with an alternating hot and cold switch is used for this purpose. Approximately 20-second intervals of repeated freezing and thawing are performed. This is done two or three times consecutively. Three such "freeze-thaws" will invariably produce a bullous reaction. Experience will determine the number and timing of freeze-thaws necessary for the desired intensity of reaction. The reaction subsides in one to two weeks, after which it may be repeated.

Some simple devices for localizing the area to be frozen with ethyl chloride are illustrated.



Ethyl chloride localizers.

COMMENT

These studies indicate that living tissue when frozen, as occurs in frost bite, should not be thawed as a temporary measure, but should be maintained frozen until permanent thawing can be accomplished. This should reduce the extent of frost damage.

The prolonged and severe temperature reduction often necessary to accomplish destruction of a superficial lesion causes unavoidable freezing at depths below the level of the disease. This unnecessary destruction may be avoided by the "freeze-thaw" technique because of the shorter time intervals of freezing.

SUMMARY

1. A cryotherapeutic technique is described and its mechanism explained.

2. It permits controlled superficial destruction with sparing of the deeper structures.

3. It has been of value in the treatment of certain hyperkeratotic and acanthotic dermatoses.

4. It is indicated that frost-bite necrosis can be minimized by not permitting thawing when refreezing may occur.

945 Fifth Ave. (21).

REFERENCE

1. Kurtin, A.: Corrective Surgical Planing of the Skin, A. M. A. Arch. Dermat. & Syph. **58**:389-397 (Oct.) 1953.

MATRICARIA (CAMOMILE) WET DRESSINGS

SAMUEL M. BLUEFARB, M.D.
CHICAGO

The symptoms produced by acute inflammation of the skin (acute dermatitis) are erythema, edema, heat, and pruritus, whereas acute inflammation affecting any other organ produces erythema, edema, heat, and pain, rather than pruritus of the involved organs.

Acute Inflammation	Acute Dermatitis
Erythema	Erythema
Edema	Edema
Heat	Heat
Pain	Pruritus

Local and topical therapy are still considered the most effective therapeutic agents in the management of most acute cutaneous diseases, the "wet dressing" being one of the most useful in dermatologic therapy. Any acute contact dermatitis, whether it is due to chemicals, plants, or physical agents, is benefited to some extent by properly applied, bland, wet dressings.

Results in Acute Dermatitis

	No. Cases	Improved	Failed to Improve
Pyoderma	7	6	1
Tinea pedis	4	2	2
Contact dermatitis	21	21	0
Seborrheic eczema	3	3	0
Stasis ulcers	6	5	1
Otitis externa	2	2	0
Infectious eczematoid dermatitis (of hands)	7	7	0
	50	46	4

In Europe, particularly in Germany, camomile flowers, used as a wet dressing, is a well-recognized form of therapy. The German or Hungarian variety is listed as the official matricaria in the National Formulary (9th edition), and this publication indicates that the dried flower head or bud is the portion of the plant to be used. The camomile plant is a member of the daisy family (Compositae) and is native to Europe, particularly to the central European countries, Germany and Hungary.

Apparently the active principle is contained in the volatile oil obtained by steam distillation and consists of azulene, sesquiterpenes, sesquiterpene furfurol, and a fatty acid. Azulene, acting as an anti-inflammatory agent,[1] is believed to produce relief of local discomfort and pain through its use as a wet dressing. The anti-inflammatory effect of matricaria was investigated by Arnold,[2] who induced inflammatory reactions with mustard oil, irradiation, tuberculin, and with medicinal agents causing exanthems. A very definite weakening in local inflammatory reactions resulted from the use of matricaria, and it was found effective in modifying the inflammation through constrictor effect on the skin capillaries.

The use of matricaria for wet dressings has never been a popular form of therapy in the United States. This is probably due to the fact that it is not stocked by most pharmacies and also because proper preparation is essential. This latter factor was solved with the recent advent of a prepared product.* This matricaria powder was used as a wet dressing on 50 consecutive patients having acute dermatitis whose diagnoses are given in the accompanying Table.

From the Department of Dermatology, Northwestern University Medical School (Herbert Rattner, M.D., Chairman).

RESULTS

Among 50 cases of acute dermatitis treated with wet dressings of matricaria powder, 46 patients showed improvement while only 4 patients failed to improve. Two patients, who were intolerant to wet dressings of Liq. alum. acetate, showed symptomatic improvement with the use of matricaria wet dressings.

SUMMARY

The results obtained in this series of cases would indicate that matricaria (camomile) powder, used in solution, is an excellent therapy for acute dermatitis. This convenient, readily available drug offers the physician another useful therapeutic agent for treatment of acute dermatoses.

* Matricaria (camomile flowers) used in the form of Chamo-Powder was supplied through the courtesy of Dome Chemicals, Inc., New York.

REFERENCES

1. Heubner, W., and Grabe, F.: The Anti-Inflammatory Action of Camomile Oil, Arch. Exper. Path. u. Pharmakol. **171**:329-339, 1933.

2. Arnold, W.: Pharmacological and Clinical Study of Camomile, Peppermint and Fennel: I. Effect on Inflammatory Processes, Arch. Exper. Pathol. u. Pharmakol. **123**:129-159, 1927.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Nathan Sobel, M.D., President

Henry Silver, M.D., Secretary

Jan. 21, 1954

Use of Absorbable Gelatin Sponge (Gelfoam) in Dermatology. Presented by Dr. Irving L. Milberg.

DISCUSSION

Dr. Frank E. Cross: Ulcers present a dermatologic problem in which I have been interested for about 20 years. I must say that I have never had much trouble with varicose ulcers of even up to 15 years' duration; but I believe that any method which is apparently as harmless and as simple as this one, and which shows results as this does, is certainly an addition to our armementarium. The treatment of varicose ulcers is a simple problem, but the sclerotic, diabetic, x-ray ulcers, or decubitus ulcers present a more difficult and more serious problem. It is there that Gelfoam (absorbable gelatin sponge, U. S. P.) powder is encouraging. This is harmless, physiologically harmless. I want to congratulate Dr. Milberg on his presentation.

Dr. John Garb: I am happy to confirm the results of Dr. Milberg's work. He was kind enough to supply me with this material. A woman aged 65 years, a diabetic, developed a painful ulcer on the inner surface of the ankle which persisted for five months following an automobile accident. The ulcer had a fibrous tissue band in the center, which her own physician hesitated to remove. I excised this pedicle and applied first 1% brilliant green, followed by oxytetracycline (Terramycin) powder. I then packed the ulcer with Gelfoam and applied a sterile dressing. This treatment was repeated once weekly. There was no pain after five days, and the ulcer healed completely in five weeks. Encouraged by this result, I sterilized the wound in the patient presented tonight with 1% brilliant green, then packed it with Gelfoam and applied a sterile dressing. She continued with the nicotinic acid (pyridine-3-carboxylic acid), 50 mg. three times a day, as a vasodilator. After one treatment the lesion improved. The improvement is gradually and steadily continuing.

I wish to ask Dr. Milberg if any investigations were done to find the reason why the other ulcer cases did not respond and if a combination with vasodilator and nicotinic acid might not have produced good results?

Dr. Alexander A. Fisher: I want to congratulate Dr. Milberg on his excellent results. I was especially impressed with the sickle-cell ulcer, which is notoriously difficult to heal. Has there been any evidence of allergic reactions? Also, what are the details in treatment—how often was the powder applied, how much was applied, is the ulcer surrounded by protective ointment, etc.?

Dr. Paul Gross: The results of this new form of therapy are convincing and Dr. Milberg is to be congratulated. I believe that this method offers definite advantages over the use of Unna's boot. The use of occlusive bandages like Unna's boot may some time give rise to autosensitization dermatitis, and therefore is contraindicated when there is evidence of infection in the ulcer itself or of the surrounding skin. I would like to know what effect Gelfoam powder has on the pain of varicose ulcers.

Dr. Abraham J. Orfuss: I have used it in three cases; two healed quite nicely. In the third, treatment had to be discontinued after three weeks because of the very severe accompanying pain, "as if the ulcer were filled with plaster of paris"—according to the patient.

DR. MABEL G. SILVERBERG: We have been using this form of treatment for three months. The whole mood of the treatment room in respect to leg ulcers has undergone a change. Nurses and patients and everybody concerned have become optimistic. We do not happen to have had patients who have complained of pain; all did very well.

DR. NATHAN SOBEL: Why does ordinary Gelfoam (pads) not seem to work when applied in these conditions, and is the powdered product available on the market?

DR. IRVING L. MILBERG: In answer to Dr. Garb, I cannot explain why those particular patients did not heal. In answer to Dr. Fisher, we have not encountered any evidence of sensitization. As far as pain is concerned, the results vary. Most patients say they have much less pain after the application of the Gelfoam powder. Those patients with severe arteriosclerosis usually have painful ulcers to begin with, and the pain may be more severe in these cases. The ordinary Gelfoam packs do not seem to get into all the crevices. The powdered Gelfoam is very easy to apply. We now have a routine treatment: We apply the protective paste around the ulcer whether or not a dermatitis is present, and where there is any evidence of infection we apply chlortetracycline (Aureomycin) powder, oxytetracycline powder, or brilliant green to the ulceration prior to the application of the Gelfoam. We have done no bacteriologic studies on the ulcers. We have found the Gelfoam useful in minor surgery. For example, when a punch biopsy is done, a No. 5 punch wound will heal completely within a week without requiring suture, when the powder is applied. The Gelfoam is usually absorbed.

Exudative Discoid and Lichenoid Chronic Dermatosis (Sulzberger-Garbe), Treated with Cortisone. Presented by DR. NORMAN B. KANOF.

D. G., a 53-year-old white man, has had a rash on his face, trunk, and extremities since early in 1952. It has persisted despite local medication, ultraviolet, and roentgen-ray therapy, and has been very pruritic.

The patient was first seen at the Skin and Cancer Unit on Nov. 5, 1953. There were numerous discrete and confluent erythematous, scaly, and infiltrated patches on the face, neck, over the chest and shoulders, on the trunk and penis, and on the upper and lower extremities. The discrete lesions were nummular in configuration.

Results of complete blood count and urinalysis were within normal limits. Serologic tests for syphilis were negative.

Microscopic examination of specimen from a lesion near the right shoulder was described as follows: "The epidermis is irregularly acanthotic and psoriasiform in type. Patchy areas of parakeratosis are present. In the upper cutis there is diffuse as well as perivascular inflammation reaction. The walls of the vessels appear edematous. The cellular reaction is pleomorphic, but not of sufficient magnitude to make a diagnosis of lymphoma.

Treatment with cortisone was begun on Nov. 17, 1953. The initial dose was 200 mg. daily. There was definite objective and subjective improvement in 48 hours, and the dose was reduced to 150 mg. daily for 5 days, then to 100 mg. daily for one week, and subsequently to 75 mg. daily, with continued improvement.

DISCUSSION

DR. NATHAN SOBEL: I have had several patients, as has Dr. Bloom, on the ward at the University Hospital, and they responded uniformly and immediately to cortisone and corticotropin (ACTH); they responded wonderfully well. They have to be kept on a maintenance dose.

1. Lichen Sclerosus et Atrophicus. 2. Hypertrophic Lichen Planus. 3. Alopecia Areata. Presented by DR. ALEXANDER A. FISHER.

Chronic Discoid Lupus Erythematosus with Mucous Membrane Lesions. Presented by DR. NORMAN B. KANOF and DR. CHARLES SIMS.

Hairy Pigmented Nevus, Presented for Suggestions for Therapy. Presented by DR. ALEXANDER A. FISHER.

Case for Diagnosis. Dermatitis Repens (?) in a Diabetic. Presented by DR. ALEXANDER A. FISHER.

Xanthelasmoid Patches with Epithelial Cysts. Presented by DR. JOHN GARB.

Extensive Excavated Sclerotic Ulcer Considerably Improved with Absorbable Gelatin Sponge (Gelfoam) Powder. Presented by DR. JOHN GARB.

Actinic Keratosis with Bowenoid Changes, Treated with Thorium X. Presented by DR. ABRAHAM J. ORFUSS.

Herpes Gestationis. Presented by DR. ANDREW G. FRANKS and DR. ERNST ROSENBAUM, (by invitation).

CHICAGO DERMATOLOGICAL SOCIETY

Julius E. Ginsberg, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

Feb. 17, 1954

Epispadias, Penile Verruca Acuminata? Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. Leonard Hoit.

History.—The patient, G. J., is a 24-year-old white man. Three years ago the patient noticed a small lesion on the dorsum of the penis. This lesion was raised and had a necrotic center. He consulted a doctor and was treated with penicillin which caused a resolution of the lesion. Four months afterward the patient noticed the presence of a similar lesion on the tip of the foreskin. This lesion ulcerated and had a purulent discharge. He was again treated with penicillin plus a sulfonamide and the discharge ceased.

Soon after this he again noticed a lesion on the dorsum of the penis. This lesion was verrucous in character and continued to enlarge, as did the lesion of the foreskin. He has since consulted many doctors without relief.

The past history was negative except for the above, plus an epispadias. The family history was noncontributory.

Physical Examination.—The penis showed a fungating mass and secondary infection at the tip of the foreskin (circumcised, Feb. 15, 1954, to get serial sections). Verrucous mass at the dorsum of the penis.

Laboratory Findings.—Urinalysis was normal. Hemoglobin 101%; white blood cell count 7,500. Serologic reactions were negative.

Punch biopsy showed verruca acuminata.

DISCUSSION

Dr. J. B. Howell, Dallas, Tex.: This is a situation where a common actor, the acuminate wart, plays an unusual role, that of a locally destructive and invasive benign epithelial tumor.

Buschke and Lowenstein, in the late 1920's or early 1930's called attention to the capacity of a long-standing large verruca acuminata to infiltrate and invade the soft tissues of the penis to unusual depths and thus mimic a carcinoma. The lesion in question is in my opinion a slow-growing, progressively destructive group of warts, and amputation may be required for complete eradication although less radical treatment will and should be tried first.

In the differential diagnosis one should consider carcinoma and granuloma inguinale, but I think that both can be ruled out.

Dr. Hamilton Montgomery, Rochester, Minn.: I want to substantiate what Dr. Howell said because we have had several South American patients in whom there has been tremendous destruction of the glans penis from verruca acuminata and in whom it was finally necessary to do partial amputation. In these cases, there was lack of histologic agreement whether the pathologic picture was that of a verruca with many mitotic figures or whether true malignant change had taken place. This was also true in patients who had had much treatment, varying from x-rays to application of podophyllum resin.

Dr. M. R. Caro: In a case of this sort it is important to perform more than one biopsy. We had a case not long ago in which several superficial biopsies showed condyloma acuminatum, but a deeper section revealed the presence of carcinoma. That could well be the case here.

Dr. Stephen Rothman: In the case presented I cannot imagine that the verruca virus alone could be responsible for the deep destruction. I agree that malignant change must be suspected.

Sarcoid with Alopecia; Sarcoidosis. Presented by Dr. Samuel Bluefarb, Dr. Harold Rodin, and (by invitation) Dr. H. K. Mitchell.

DISCUSSION

DR. ADOLPH ROSTENBERG: The combination of alopecia with sarcoidosis is, in my experience, unusual. The Illinois staff will recall that a few weeks ago we saw a Negro woman who had diffuse alopecia of the scalp plus the bone and lung changes of systemic sarcoidosis. On the skin there were lesions typical of sarcoidosis but there was also some suggestion of lupus erythematosus. The biopsy from a skin nodule was reported as compatible with sarcoidosis. The alopecia in this woman was very diffuse and did not appear to be a consequence of local infiltrates such as in the woman presented today. I do not recall ever having heard of such a combination nor did Dr. Senear, to whom I showed the case at the time she was in our clinic.

DR. THEODORE CORNBLEET: It seems to me that atrophy of the skin can and does occur in sarcoidosis. Dr. Ormsby's book contains a picture of a patient with a lesion quite similar to this one. Cortisone has a temporary favorable effect on sarcoid lesions. Hydrocortisone ointment might stay the extension of the lesion farther into the scalp and thus prevent a larger area of permanent alopecia.

DR. WILLIAM SLINGER, Rockford, Ill.: I should like to ask Dr. Rostenberg what he feels the present status of the Kveim test is. When I was in Oslo, Dr. Danbolt and the other men told me very certainly that they did not believe that any two groups of observers had produced the Kveim reaction with extracts of spleen and liver or had presented adequately controlled experiments.

DR. STEPHEN ROTHMAN: In the experience of our chest department, the Kveim test is an absolutely specific test. I do not believe that extracts of normal spleens would ever yield this reaction.

DR. ADOLPH ROSTENBERG: It is a matter of historical interest that recently Danbolt reported (*Schweiz. med. Wchnschr.* **52**:138, 1946) on Boeck's very first case of sarcoid. The man was 80 years old at the time of the report and had been admitted to the hospital for a kidney complaint which turned out to be a hypernephroma, from which he died. A necropsy was done, and there was no evidence of sarcoidosis grossly or histologically in any of the internal viscera. On the skin where there apparently had been sarcoid lesions at the time Boeck saw the man in 1896, there were faint yellowish areas of atrophy plus telangiectasis. It is interesting that the Kveim test was still positive.

While there is no doubt that the Kveim test has a theoretical rational basis, like the Frei test, it does not seem to be of great practical value. First, there is no standarized source of antigen; consequently one has to make his own, and there is apparently great variability in potency. For example, we made some, using lymph nodes from patients who had all the earmarks of systemic sarcoidosis, and yet the vaccine did not yield positive reactions in any subject. The second drawback from a practical point of view is that apparently, for reasons that are somewhat obscure, a positive reaction may be inordinately long delayed—months to years. It is obvious that a test that will show up only after this length of time is not of too much value in the routine diagnosis of patients.

DR. M. R. CARO: I should like to comment on the presence of atrophy in sarcoidosis. In sections of sarcoid there are densely packed masses of epithelioid cells that often fill the corium, and this is bound to result in atrophy. If the lesion should be present on the scalp, there would certainly be a bald spot at the site. Sarcoid very seldom affects the scalp and therefore we do not see alopecia very often.

DR. M. H. EBERT: Since the Kveim test has been mentioned, it is interesting to note that extracts made from lymph nodes of patients with well authenticated sarcoidosis, even though they have been prepared with all proper precautions, are not equally efficient in the production of the Kveim test. Some excellent work on this subject has been done at the University of Chicago Medical Department. The annular type of sarcoidosis of the skin is not rare. I agree with Dr. Caro that when the central infiltrate absorbs, it is bound to leave a scar. The lesions in the scalp that were present today were also annular lesions. However, the amount of scarring in the center of these lesions was unusual.

DR. S. M. BLUEFARB: Our purpose in presenting this case is threefold. When this patient was presented at the Cook County Hospital the attending staff all agreed that (1) patchy alopecia associated with sarcoidosis is rare; (2) the annular lesions are an unusual feature in sar-

coidosis, and (3) the hypersplenic syndrome is present in this patient. Hypersplenism signifies a breakdown of the elements in the peripheral blood from functional overactivity of the spleen. Hypersplenism may be primary or secondary. The secondary type may be due to various diseases such as congestive splenomegaly (Banti's syndrome), lipid diseases, inflammatory splenomegalies (syphilis, sarcoidosis), collagen diseases, and the lymphoblastomas. The criteria for making a diagnosis of hypersplenism are enlarged spleen, depletion of blood elements in the peripheral blood, as manifested by anemia, leucopenia, thrombocytopenia, and demonstration of unimpaired bone marrow production.

This patient has an enlarged spleen, anemia, leucopenia, thrombocytopenia, and normal bone marrow. The hypersplenic syndrome is important to the dermatologist since the first manifestations may appear on the skin. The pallor and glossitis are due to anemia, ulcerations in the mouth and on the skin, to leucopenia and purpura, and to thrombopenia.

In this case the hypersplenism was corrected by removal of the spleen but this had no effect on the sarcoidosis which is still present although the blood picture is now normal.

Scrofuloderma. Presented by DR. ROBERT E. BLOOM (by invitation).

History.—A 35-year-old female packing house worker's chief complaint began 10 years ago as firm, painless nodules which enlarged slowly, then ulcerated, draining a purulent fluid. The lesions would then heal with scarring and hyperpigmentation, the whole course of events requiring a period of several months.

The family history is significant in that the patient's brother came to live with her in 1948 and died in 1952 after an operation for tuberculosis of the spine.

Physical Examination.—When first seen, on Feb. 1, 1954, at the University of Chicago Clinics, examination of the skin revealed well-healed linear scars showing bridging and papillomatous excrescences on both sides of the neck and in the right axilla. A few 1 to 2 cm. nodules could be palpated beneath several of the scars. Anteriorly on the left side of the neck an oval 5 mm. undermined ulcer with a necrotic base drained a thin creamy exudate. This lesion could be probed posteriorly to a distance of 2 cm.

The remainder of the physical examination was negative. The patient is seven months pregnant.

Laboratory Findings.—Laboratory work revealed normal urinalysis, blood count, and fasting blood sugar. The Kahn test was negative.

Chest x-ray revealed no evidence of tuberculosis. There were no soft tissue calcifications in the neck. Mantoux test was strongly positive 1 : 10,000.

Culture of the lesion revealed hemolytic Staphylococcus aureus and Staphylococcus albus. Direct smear was negative for acid-fast bacilli. Results of culture and guinea pig inoculation for acid-fast bacilli have not been reported.

Biopsy: The epidermis is acanthotic, edematous, and deeply pigmented, and there is a superficial erosion. There is a chronic inflammatory infiltrate in the upper corium, and in the deeper corium there is an area of tuberculoid granulation tissue with epithelial cells, Langhans giant cells, and lymphocytes. With Ziehl-Neelsen stain no acid-fast bacilli were seen.

DISCUSSION

DR. ROBERT E. BLOOM (by invitation): I should like to mention some studies done with C^{14}-labeled isoniazid done by R. H. Ebert, Barclay, and Roth at the University of Chicago Clinics. In addition to finding that the drug was freely diffusible into caseous foci, large amounts were stored in the skin. In fact the skin seems to act as a major storage depot of the drug.

With regard to therapy, some conclusions were reached at the February, 1954, Conference of the Section on Chemotherapy of the Veterans Administration as to the most effective method of using the new antituberculous agents. It was concluded that isoniazid should be used first, streptomycin and paraaminosalicylic acid being reserved for later possible complications. It was further agreed that isoniazid should be used continuously rather than intermittently for at least six months and preferably a year. Since isoniazid acts specifically on the tubercle bacillus and calciferol on the host tissue, we plan to use this combination of drugs in treating our patient.

Dermatitis Herpetiformis. Presented by Dr. Stephen Rothman and (by invitation) Dr. Stanley M. Mesirow.

History.—This 61-year-old housewife was first seen at the University of Chicago Clinics on Dec. 11, 1950, with the complaint of a recurrent eruption during the previous six years. The eruption was described by the patient as pea-sized blisters occurring mostly on the upper back, on the chest, under the breasts, and on the scalp and accompanied by an intense burning sensation at the onset and later by itching. The blisters would later rupture and frequently were followed by pigmentation. She had taken an unknown sulfonamide drug about six months previously and showed marked improvement. However, use of the drug was discontinued because of severe gastric upset.

Physical Examination.—There was a mottled brown pigmentation of the neck, shoulders, back, and anterior chest, under the breasts, and on the abdomen and upper arms. A few scattered reddened papular lesions were also present in these areas and on the scalp. On subsequent visits, grouped vesicles appeared in these locations.

In May, 1951, she was given sulfapyridine (3 gm. daily) and has continued this medication in varying dosages to the present time with satisfactory control of her eruption and subjective symptoms.

Laboratory Findings.—Urinalysis: No albumin, sugar, or blood. The Kahn test was negative. The stools were negative. White blood cell count was 16,800; differential distribution, polymorphonuclears 40, large lymphocytes 0, small lymphocytes 58, monocytes 2, eosinophiles 0, and basophiles 0.

Dermatological Pathology.—The epithelium appears normal apart from slight intercellular edema in some places. There is subepidermal edema, amounting in one place to a small vesicle. Here there is a loose infiltrate of lymphocytes, and around the small vessels of the upper half of the corium there are also edema and perivascular infiltrate with a few eosinophiles.

DISCUSSION

Dr. M. H. Ebert: If I saw this case for the first time today in my office without taking a history, I doubt very much if I could make a diagnosis of dermatitis herpetiformis from the lesions today. There are no bullae; there are a few vesicles on an erythematous base, and there are few papules. There is very little pigmentation. However, the patient complains of intense itching. From the history we learned that this patient has been under sulfapyridine therapy, which accounts for the paucity of lesions. She has had this disorder in one form or another for 10 years. I thought the distribution was unusually interesting, in that the lesions have always been confined to the upper half of the trunk, the face, and the scalp. It is rather unusual for dermatitis herpetiformis of this duration to show such a limited distribution.

In the differential diagnosis, one would consider an unusual Hailey and Hailey disease. However, there is no familial history, and the distribution is too widespread for this disorder. Pemphigus can be ruled out by the absence of mucous membrane lesions over a period of 10 years, as well as by the multiformity of the lesions. One must finally consider multiform erythema of toxic origin. The amount of itching and burning she complains of would be very unusual. I believe the biopsy sections enable us to make a histologic diagnosis of dermatitis herpetiformis. The vesicles were subepidermal and the infiltrate contained a large number of eosinophiles. The hemogram showed no eosinophilia. However, this is probably due to present treatment. There is no record of iodide test having been tried. It would be interesting to see whether it would be positive or not. The excellent response to sulfapyridine makes the diagnosis of dermatitis herpetiformis most likely. The case is unusual in the limitation of the lesions to the upper half of the body for such a long period.

Dr. Otto C. Stegmaier, Davenport, Iowa: I had seen this patient in 1951 and I think I can answer Dr. Ebert's question regarding the iodide patch test. The internist gave her intravenous injections of sodium iodide, and she developed massive bullae on the arm and neck within 12 hours after the injection. She definitely has dermatitis herpetiformis.

I should like to have Dr. Rothman's comment as to how he is handling her with sulfapyridine and whether he has used the enteric-coated capsule or some other kind, since she had gastric upsets on sulfapyridine while under my care.

DR. HAROLD SHELLOW: There was some question concerning the sulfapyridine, which leads me to mention a case that had been under observation periodically for some 10 years, finally becoming completely refractory to sulfapyridine. The patient was then put on a regimen of hydrocortisone by mouth, receiving 20 mg. four times a day, with a very satisfactory response which led to a complete remission. It has been found that he has been free of the itching and of the eruption with one 5 mg. tablet daily.

DR. THEODORE CORNBLEET: With Hailey and Hailey's disease suggested as a possible diagnosis, it might be well to try chlortetracycline (Aureomycin) as a therapeutic test. I find two capsules (250 mg. each) a day are enough to control my patient's eruption.

DR. STEPHEN ROTHMAN: The discussion by Stegmaier brought out clearly that beyond doubt this patient has dermatitis herpetiformis. I do not believe a therapeutic test with chlortetracycline (Aureomycin) to exclude Hailey and Hailey's disease is necessary in this case because the therapeutic test with sulfapyridine, among other pieces of evidence, has amply proved that the diagnosis of dermatitis herpetiformis is correct. The late Dr. Hopkins told me once that he diagnosed dermatitis herpetiformis mainly on the basis of whether the case responded promptly to sulfapyridine or not. Our patient was known to demonstrate that sulfapyridine can be given for years without side-effects and without decreasing efficacy. We have patients now under observation who have been taking sulfapyridine for 10 years and still are able to control their disease perfectly. I am very much interested to hear that there are cases in which the effectiveness of the drug has decreased. We check the urine and white cell count quite frequently for one to two years, but if no leucopenia or kidney damage has developed in the first year we check only four times a year.

The suppressive effect of sulfapyridine very much reminds me of the suppressive effect of sulfonamides in experimental infections with lymphogranuloma venereum virus. Rodaniche, at the University of Chicago, found that mice can be protected with sulfonamides against intracerebral inoculation of this virus. But if the brain tissue of these protected animals is injected into healthy mice they will die of lymphogranuloma venereum infection (Rodaniche, E. C.: Sulfanilylguanidine and Sulfanilamide in the Treatment of Lymphopathia Venereum Infections of Mice, *J. Infect. Dis.* **70**:58-61, 1942). I wonder whether a similar virostatic effect of sulfapyridine operates in dermatitis herpetiformis.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Brunsting has a great many patients who have gone 10 to 12 years on sulfapyridine. Once we know what their tolerance is, we do not worry about continuing with the drug indefinitely.

DR. F. J. SZYMANSKI: Dr. Finnerud and I have a patient with the worst case of dermatitis herpetiformis that we have ever seen. For a period of five or six years he was well controlled with a small maintenance dose of sulfapyridine. Unfortunately, sulfapyridine lost its effect, and the patient was miserable until he received sulfoxone (Diasone) which controls the eruption and itching fairly well.

DR. M. J. REUTER, Milwaukee: I have had one patient with herpes gestationis whom I followed through five pregnancies. With the first and second pregnancy she did well with sulfapyridine; with the third pregnancy the disease was not controlled with the drug. In the last two pregnancies sulfapyridine was completely ineffectual, but the disease was controlled with corticotropin and cortisone. I might add for the record that there has been no adverse effect upon the offspring.

Pseudoxanthoma Elasticum (Associated with Angioid Streaks of the Retina).
Presented by DR. OTTO C. STEGMAIER, Davenport, Ia.

History.—L. A., a 28-year-old white garment worker, was first seen Jan. 30, 1954. Her lesions were first noted at the age of 10 years. They have gradually coalesced over the years to form an asymptomatic plaque about the neck. She apparently is unaware of any other similar lesions. A painful growth has been noted on the left shoulder for five years. Her general health is good except for anemia. One of three siblings, aged 12, is now developing a yellow plaque on the neck. The history of the parents is negative.

Physical Examination.—Examination reveals a well developed, pale woman with yellowish plaques involving the neck, the axillae, and the sternal and cubital areas. There is questionable

involvement of popliteal space. The groin is normal. Mucous membranes of the mouth failed to reveal any yellow lesions. The most developed plaque covers the entire neck, extending down over the clavicles. It consists of a hyperelastic thickened yellowish confluent plaque, with pigmented follicular openings. There is a 0.5 by 3 cm. linear elevated firm nodule over the left shoulder.

Ophthalmoscopic examination reveals typical angioid streaks, pigmentation, and choroid lesions.

Laboratory Findings.—Biopsy from the right side of the neck shows swelling and fragmentation of the elastic fibers. Fibroma was the diagnosis from biopsy of the left shoulder.

DISCUSSION

DR. F. J. SZYMANSKI: As all of you know, pseudoxanthoma elasticum is not an innocuous condition affecting only the skin. It is a disease involving the elastic tissue in various parts of the body. Balzar, who described the first case of pseudoxanthoma elasticum, reported yellowish nodules on the endocardium at autopsy of his patient. These nodules showed the same changes in the elastic fibers as are seen in the involved skin. More recently H. H. Wolff and his co-workers reported a very unusual case in the *Archives of Disease in Childhood* (**27**:82-88 [Feb.] 1952) of a boy 5 years old with pseudoxanthoma elasticum and intermittent claudication, loss of pulsation in the distal arteries of the limbs, calcification in the proximal arteries, and vascular changes in the fundus. The patient's brother has pseudoxanthoma elasticum of the skin, calcification of the femoral artery, intermittent claudication, and changes in the fundus at the age of 25 years.

All of us are aware of the association of angioid streaks with pseudoxanthoma elasticum. However, you may be surprised to learn that four cases of osteitis deformans associated with angioid streaks were reported by Terry (*Tr. Am. Ophth. Soc.* **32**:555, 1934). In addition, he surveyed the literature, and of 104 cases of angioid streaks 9 demonstrated Paget's disease of bone. Terry was unable to find a case of pseudoxanthoma elasticum with osteitis deformans. However, Woodcock showed a case with pseudoxanthoma elasticum, angioid streaks, and osteitis deformans to the Cleveland Dermatological Society (**65**:623 [May] 1952). Some of you may ask, "What does osteitis deformans have to do with a disturbance of the elastic tissue?" Just recently certain observers have become aware of multiple arteriovenous fistulae running throughout the hypertrophied bones of osteitis deformans. As far as I know, no biopsies or histologic studies have been done on those arteriovenous aneurysms, but it occurred to me that these fistulae could be due to a degeneration of the elastic tissue.

A final word about prognosis. The skin changes in this disease are not very important except from a cosmetic standpoint. The angioid streaks are far more serious. There is an impairment of vision in all of the patients with angioid streaks, sometimes leading to blindness.

DR. STEPHEN ROTHMAN: Lobitz and Osterberg have shown by both microincineration and chemical analyses the accumulation of huge amounts of calcium in such cutaneous lesions. (Lobitz, W. C., Jr., and Osterberg, A. E.: Pseudoxanthoma Elasticum: Microincineration, J. Invest. Dermat. **15**:297-298, 1950). This fits well with Dr. Szymanski's comment on generalized calcifying vascular changes in this disease. It is a most challenging task to find out why some degenerative processes are connected with calcium deposition and why others are not.

DR HAMILTON MONTGOMERY, Rochester, Minn.: Pseudoxanthoma elasticum and angioid streaks are closely related but may occur independently of one another. There is a localized calcinosis, as Lobitz and Osterberg and also Finnerud and Nomland showed. It is interesting to have the discussers bring out the systemic nature of pseudoxanthoma elasticum. There have not been many cases in which the cholesterol and blood lipids have been studied, but I would prefer to regard the present acrosclerosis as a coincidental finding. One can find calcinosis in both dermatomyositis and scleroderma, and occasionally the calcinosis will be just as prominent as that seen in pseudoxanthoma elasticum.

DR. ADOLPH ROSTENBERG: I want to make one comment on the systemic complications of pseudoxanthoma elasticum. I saw a young woman at Hines Hospital, under 35 years of age, who had a very diffuse pseudoxanthoma elasticum with angioid streaks. She had had a gastrectomy and was told that she had the same involvement in her stomach as she had in the skin.

We had no opportunity to work up the case. We had only her story that similar pathologic alterations were found in the stomach as in the skin. She was a very uncooperative patient and left against advice.

DR. OTTO STEGMAIER, Davenport, Iowa: This may answer some of the questions. The illustration presented with this woman was from Wilmer's "Atlas of Ocular Fundi." It mentioned one case in a 26-year-old man who died five years after the onset of the disease and autopsy showed localized calcification of skin and muscles and also amyloid deposits in the kidneys and other organs. The serial sections did not reveal abnormalities of the elastic tissue in the eye. This patient is being subjected to a general work-up. If I have any more information, I will report it later.

Multiple Telangectasias Plus Acrosclerotic Changes of the Extremities with Dupuytren's Contracture. Presented by DR. A. ROSTENBERG.

History.—The patient, E. W. O., a 58-year-old white man entered the hospital on Jan. 16, 1954 because of numbness in his hands and legs and extreme sensitivity to cold in his hands for the past two years. Upon exposure to low temperatures, his hands became very white as well as painful. In addition, he complained of shooting pains in his legs for a similar period. The patient gave a history of excessive alcoholic intake. He had had some orthopnea, exertional dyspnea, and paroxysmal nocturnal dyspnea over the past year. His stools have been acholic for a week prior to admission. He had had several previous hospitalizations for alcoholism, ulcerations of the lower esophagus, and chronic gastritis.

Physical Examination.—Blood pressure was 110/60; pulse rate 120 and regular. The forehead, face, and neck were covered with large telangiectasia. There was a Grade II retinopathy. Mucous membranes were pale. Chest was emphysematous. Liver was palpable 8 cm. below the right costal margin and was firm and tender. Spleen was not palpable. A large right indirect inguinal hernia was noted. There was a 3+ sacral pitting edema. Deep tendon reflexes were hyperactive. There was a hypesthesia in a glove and boot distribution.

Examination of the skin revealed the above-mentioned angiomata over the face, forehead, and fingers, with a few on the upper trunk and tongue. Examination of the hands revealed a tightening of the skin of all fingers, with slight evidence of attenuation and a peculiar pallor of most of the fingers. The skin felt adherent to the overlying structures. In addition, there appeared to be Dupuytren's contracture of the left ring finger. There were similar although less marked changes of the toes.

Laboratory Findings.—Urinalysis essentially negative. Blood count revealed a marked hypochromic anemia with a moderate leucocytosis. Liver function tests revealed an increased sulfobromophthalein sodium retention and an elevation in the serum globulin.

Serologic reactions were negative.

X-ray of the chest revealed cardiac enlargement, pulmonary congestion, and a slight degree of pleural effusion at the right base. Gastrointestinal series revealed a narrowed distal segment of the esophagus consistent with scleroderma, although benign stricture or carcinoma should be considered.

Since admission, the patient has received three blood transfusions and his hemoglobin has risen from 4 to 7.5 gm. His decompensation had been controlled, and for the past two weeks he has received daily methacholine (Mecholyl) chloride iontophoresis with a marked improvement of the skin changes in his hands.

DISCUSSION

DR. OTTO STEGMAIER, Davenport, Iowa: In addition to the multiplicity of diagnoses with which this patient was presented, I think there were two important points that should interest us. The first is the multiple telangiectasias over the face, upper chest, and hands, suggestive of pulsating angiomas associated with hepatic disease. This condition was first described by Snell and Williams, and it has been written up extensively in addition to other types of telangiectasia by W. Bean, an internist formerly at Cincinnati, now in Iowa. He has an idea, since angiomas occur in pregnancies and in hepatic disease, that there is a steroid relationship. I do not know of any cases that have appeared under corticotropin (ACTH) or extensive cortisone therapy. In the second place, I believe that this patient has Raynaud's disease with

secondary scleromatous changes about the hands. The reason I say Raynaud's disease rather than scleroderma or acrosclerosis is that the sclerodermatous change is limited to the areas where the Raynaud phenomena take place.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This is the most extensive case of pulsating angiomas that I have seen and is much more extensive than cases described by Williams and Snell (*Arch. Int. Med.* **62**:872, 1938). In order to feel the pulsations one must exert very light pressure. The patient, in addition, has acrosclerosis with Raynaud's phenomena. I do not believe that the two conditions are related, and this is the first time I have seen the combination of the two conditions.

DR. THEODORE CORNBLEET: Some time during 1953 there appeared in *Pflügers Archiv* a good histological study of these spider nevi, showing them to be arteriovenous aneurysms.

DR. ADOLPH ROSTENBERG: I should like to thank the various discussers. Dr. McCraney and I felt there was some pulsation in some of the lesions. I think the case is of interest because it is rather unusual to see such a large number of telangiectases. The man had some on the tongue as well. I do not believe that the changes in the hands are causally related to the liver disease. I certainly have never seen the combination of multiple telangiectases (some pulsating angiomas) plus acrosclerotic changes limited to the fingers, nor have I heard of it. As to the proper label, whether it is a Raynaud's disease or true acrosclerosis, I do not know.

Secondary Syphilis. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. HAROLD MARKS.

Tuberculoderma? Sarcoidosis? Presented by DR. THEODORE CORNBLEET and (by invitation) DR. SIDNEY BARSKY and DR. HAROLD MARKS.

Lupus Erythematosus, Chronic Discoid. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. H. K. MITCHELL.

Ichthyosis Hystrix. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. LEONARD HOIT.

Cutaneous Blastomycosis. Presented by DR. ADOLPH ROSTENBERG JR. and (by invitation) DR. SIDNEY J. KAPLAN.

Hypertrichosis Treated with the High-Frequency Current. Presented by DR. WILLIAM A. ROSTENBERG.

Case for Diagnosis: Spotted Diffuse Melanoderma. Presented (by invitation) by DR. FREDERICK D. MALKINSON.

Facial Granuloma with Eosinophilia? Presented by DR. ALBERT H. SLEPYAN and (by invitation) DR. MAURICE WALD.

Late Syphilis, With Residue of Late Cutaneous, Ocular, Osseous, Cardiovascular, and Possibly Pulmonary Involvement. Presented by DR. FRANCIS E. SENEAR, DR. GEORGE FLEMING (by invitation), and DR. LOUISE TAVS.

Julius E. Ginsberg, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

March 17, 1954

Lupus Erythematosus Sine Lupus Erythematosus, with Positive L. E. Cells and Nephrosclerosis. Presented by DR. THEODORE CORNBLEET, DR. SIDNEY BARSKY, and (by invitation) DR. H. K. MITCHELL.

Lupus Erythematosus. Presented by DR. THEODORE CORNBLEET, DR. SIDNEY BARSKY, and (by invitation) by DR. H. K. MITCHELL.

Lupus Erythematosus with Depigmentation. Presented by DR. SAMUEL BLUEFARB, DR. HAROLD RODIN, and (by invitation) DR. H. K. MITCHELL.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: The patients presented here are a far cry from the textbook picture of systemic lupus erythematosus. As the L. E. test is applied more and more to the investigation of patients with unusual arthritic and renal syndromes, it is evident that some forms of systemic lupus erythematosus never show cutaneous reactions, and, secondly that the course of the disease may be long drawn out through years of remissions and periodic relapse. I have seen several instances in which patients have had a severe degree of mutilating arthritis and others with advanced renal disease which were the only signs of lupus erythematosus. I do not believe that steroid therapy should be instituted solely on the basis of a positive

L. E. test. These hormones will control fever, arthralgia, and, to some extent, effusions, and they will evoke an improvement in general well being. In some patients it is advisable to treat periodically with cortisone or corticotropin (ACTH), and at the same time not to lose sight of the need for blood transfusions, high protein diet, measures of physical therapy, and, above all, a program of rest. In the management of younger women who experience aggravation during the menstrual cycle, the use of estrogens in quantity sufficient to suppress the menses may reduce the need for steroid therapy.

It is becoming apparent that the management of patients with systemic lupus erythematosus, in general, is an individual problem; inasmuch as we know little or nothing about the etiologic factors concerned, our chief efforts must be directed toward symptomatic control.

DR. ADOLPH ROSTENBERG, JR.: As Dr. Brunsting said, our point of view about lupus erythematosus, particularly systemic lupus erythematosus, is changing. Of course, one of the prime events responsible for this change was the discovery of the L. E. cell, and the lupus factor in the serum. When the test was first reported it proved to be quite specific for L. E., but recently Walsh and Zimmerman have reported finding the L. E. factor in severe cases of penicillin reactions. As Dr. Brunsting mentioned, this woman is in remission and the L. E. cell is not found. Gold and others have written extensively on sensitivity as a cause of L. E. All of these points then raise the question: Is the L. E. phenomenon an expression of a particular kind of sensitization reaction which may have more than one clinical expression, or is it a response to a particular morbid entity, namely L. E.? It would be of some importance to have accurate statistics on the incidence of acute disseminated lupus erythematosus. Is it increasing with the increasing use of drugs which are strong sensitizers? I think it would be of interest where we have a marked sensitivity reaction that has some of the appearance of polyarteritis nodosa, to search for the L. E. cell or factor. This might give us some insight as to the pathogenesis of lupus erythematosus.

DR. HENRY E. MICHELSON, Minneapolis: Dr. Brunsting brought out the importance of management, not necessarily treatment, in handling L. E. patients. There is no question we have advanced a great deal in diagnosis in this condition in the last five years, and the therapy is also improving, but there is still room for advances. I do not believe that the use of antibiotics has been thoroughly evaluated, and the question of what to do when such a patient has a positive blood culture is important. In a recent debate with the Department of Medicine I held that, even though one had a positive blood culture with an indicated antibiotic, the treatment with the antibiotic without the use of the steroids would be valueless, and that proved to be the case. I believe we should consider doing blood cultures more frequently in the systemic cases.

DR. THEODORE CORNBLEET: We used to see numbers of patients in the medical wards with and without skin lesions, problem cases in which lupus erythematosus was thought of as a diagnosis. The internists no longer ask our opinions. Through this experience we came to be impressed with a number of variable syndromes, with all degrees of severity and mildness. Many of these patients with lupus erythematosus do not die. They just get ill at unpredictable intervals with something less than complete recovery in between. They just carry on, not being quite invalids.

DR. H. H. RODIN, South Bend, Ind.: Because of recent reports in the literature that L. E. cells have been found associated with severe drug eruptions, particularly penicillin, we have carried out L. E. studies on the last 12 cases of penicillin reactions that have been admitted to our ward. In all cases the examinations were negative.

Erythema Nodosum. Presented by DR. THEODORE CORNBLEET, DR. S. BARSKY, and (by invitation) by DR. H. MARKS.

History.—This 43-year-old Negro woman was in good health until two weeks prior to admission, when she had a "cold" associated with pain in hips and knees. As the upper respiratory infection subsided the patient developed discrete painful subcutaneous nodules on the extensor surfaces of both arms, and pain in the pretibial areas. She gives a history of taking 666 (a preparation containing antipyrine, citric acid, magnesium sulfate, and ammonium chloride) for her cold. The past history and the family history are noncontributory.

Case for Diagnosis (Erythema Induratum: Nodular Vasculitis?). Presented by DR. OTTO C. STEGMAIER.

History.—M. W., aged 33, Polish D. P. woman, presents nodules, ulcers, and large purplish red areas of induration involving the lower legs symmetrically. The condition has been present for the past 10 years. It disappears in the summer and reappears in the cold winter months. Prior to her entry to the United States five years ago, a chest film was negative.

Laboratory Findings.—A recent chest plate is negative. Intradermal tuberculin test (Parke, Davis PPD, intermediate strength) was positive. Sedimentation rate was 26 mm. per hour (Cutler method, normal for women 0 to 15).

An excision biopsy specimen of an area of induration was interpreted as panniculitis. The slide is presented.

Pulmonary Hilar Syndrome: Erythema Nodosum and Sarcoidosis? Presented by DR. ADOLPH ROSTENBERG JR., and staff.

History.—D. T. G., a 30-year-old man, complained of intermittent nausea, headaches, and fever for four to five weeks, arthralgia and muscular aches of eight days' duration, swelling of both feet for five days, and development of nodules in the feet, legs, and forearm, with coughing of one day's duration. Patient had been taking numerous medications, including sulfisoxazole (Gantrisin), penicillin, Co-Pyronil (pyrrobutamine with thenylpyramine and cyclopentamine hydrochloride), phenobarbital, atropine, neostigmine (Prostigmin) for a sluggish bowel, and thyroid extract as much as 3 grains (0.2 gm.) daily for a year.

Physical Examination.—On admission, examination revealed a slightly obese white man in a moderately acute attack, complaining of the above-mentioned symptoms. Examination of the abdomen revealed slight tenderness of the right upper quadrant, while that of the skin revealed numerous coin-sized, erythematous, and slightly tender nodules on the extensor surface of each forearm and on the dorsum of the soles, feet, ankles, and lower leg.

Laboratory Findings.—Positive findings revealed a persistently elevated sedimentation rate ranging from 15 to 25 mm. per hour, and repeated chest x-rays revealed enlarged hilar mediastinal lymph nodes as well as a dense nodule in the left sixth interspace consistent with the diagnosis of a tuberculoma, but no calcification, no cavitation within the density, and it was considered to be consistent with the diagnosis of erythema nodosum or sarcoidosis. Laminogram of the nodule was negative. Skin tests were negative to histoplasmin, blastomycin, coccidioidin, and first and second strength PPD.

Since admission approximately some three weeks ago, the cutaneous lesions have shown a tendency toward involution. Recently a systolic murmur has been noted. Treatment to date has been limited to salicylates and antispasmodics.

Recovery from Relapsing Febrile Nonsuppurative Panniculitis (Weber-Christian Disease). Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. ALLAN L. LORINCZ.

History.—W. S., a 51-year-old white woman, was presented previously before this Society on Nov. 21, 1951, because of her severe Weber-Christian disease associated with lupus erythematodes disease.

Subsequently, while the patient was on a regimen of bed rest, autohemic injections, vitamins, and small doses of quinine, undiminished activity of the disease persisted for about four months, with many new nodules of panniculitis appearing, and with malaise, tachycardia, severe leucopenia, and fever. Then while she was still on the same program of management, the disease gradually began to subside, until by Oct. 1952, the patient was afebrile and had only very occasional small new subcutaneous nodules, and her white blood count became normal. As the former panniculitis lesions involuted, 1 to 2 in. (2.5 to 5 cm.) areas of atrophy of subcutaneous fat tissue became evident and gave the involved regions a strikingly scalloped appearance.

In March, 1953, the patient developed acute appendicitis, which perforated. Appendectomy was done, and prompt recovery followed an uneventful postoperative course.

Physical Examination.—At the present time the patient continues to be afebrile and is in a very satisfactory general state, with only about a half dozen small, hard, subcutaneous nodules remaining on the extremities and trunk.

Laboratory Findings.—Hemoglobin 15.0 gm.; white blood cell count 8,300, with normal differential count. Sedimentation rate 12 mm. per hour. Urinalysis is entirely normal.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I have been much interested in erythema nodosum for a long while because of the controversy concerning the position of the disease. Is it a disease or is it a symptom of another disease? I think in the majority of cases one is unable to point out the direct relationship to an underlying condition. I think that many times the evidence is presumptive. I have been unable to find the so-called Miesscher granuloma in many slides; I think it was 3 in 20 cases.

DR. HARRY R. FOERSTER, Milwaukee: It is probably a mistake, on cursory examination, to differ with the presenter, who has had an opportunity to study his case. However, I could not substantiate either diagnosis in Case 2. I thought there was too little infiltration, too much inflammation, and rather numerous small lesions for erythema induratum. I did not think the lesions as deeply indurated as commonly observed in erythema induratum. My impression favored consideration of an indolent pyogenic infection. As regards nodular vasculitis, I do not recall having seen a case so diagnosed that presented ulceration. I would expect firm, deep-seated, sharply marginated, nonsuppurative indolent inflammatory plaques, few in number or possibly single. In the histologic section I did not find the deeply situated cellular infiltrates one looks for in erythema induratum. The mixed leucocytic and round cell infiltrate with a few giant cells can, I believe, be found in old pyodermas, as in nonspecific chronic inflammations.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Erythema nodosum and hilar infiltration may occur in the presence of sarcoidosis. In the early stages, the exact diagnosis may be impossible. If lymphadenopathy is present, a node may be excised for biopsy. This may give more information than a biopsy of one of the nodose lesions of the skin.

In the so-called rheumatoid form of erythema multiforme, I have been impressed by the exceedingly high sedimentation rate of the erythrocytes, which continues to climb for several weeks after the acute symptoms have subsided.

DR. THEODORE CORNBLEET: This patient had, coupled with the skin lesions, swelling of the ankle joints. We have seen several such associations on the wards from time to time. We were not entirely satisfied with the diagnosis of erythema nodosum, but it seems to fit best. The swelling of the joints does not seem to be that of rheumatic fever, nor does the patient have rheumatoid arthritis. Some of these episodes, nodes and ankle swelling, repeat themselves several times in the patient's career. I do not know where to put this syndrome other than under erythema nodosum. The L. E. cell is absent.

In connection with Dr. Brunsting's remark on sedimentation rate, these patients also have disturbances of the normal blood protein pattern. This particular patient had a rather high total protein level explaining the disturbed sedimentation rate. The gamma globulin is about as high as I ever saw it, 4.5 gm. per 100 cc. When we saw the first report we thought it was in error, but a second determination corroborated the initial value, so I think we can accept it.

DR. ADOLPH ROSTENBERG, JR.: I would, of course, agree wholeheartedly with the various speakers that erythema nodosum is a very interesting disease and one about which we have very much to learn. Erythema nodosum lesions are seen in tuberculosis, in lymphogranuloma venereum, and in streptococcal and many other infections. There could be an idiopathic erythema nodosum, but all that probably means is that some as yet unidentified micro-organism is acting as the offending allergen. It presumably would still be an indication that the host has become responsive to some allergen. A bilateral hilar lymphoma syndrome has been described. This consists of erythema nodosum, usually on the legs, plus hilar x-ray shadows suggestive of sarcoidosis.

What is tuberculous erythema nodosum? It is erythema nodosum in which the patient ultimately develops tuberculosis. The patient usually develops a caseous tuberculosis. Skiold and others have pointed out that erythema nodosum found with bilateral hilar nodes is generally nontuberculous, whereas that with unilateral hilar involvement is usually tuberculous. The

question arises: When you see erythema nodosum with bilateral nodes, of what disease is it indicative? In some cases it is indicative of sarcoidosis. In others it may mean an idiopathic E. N. I think this man should be watched for the development of sarcoidosis. Another point favoring this belief is that this patient was negative to every cutaneous test with all the standard micro-organismal antigens. To sum up, I do not think we should simply say this is a case of erythema nodosum, but we should examine such a patient to determine if some systemic infection can be established as the cause.

DR. STEPHEN ROTHMAN: I agree that the cause of nonsuppurative febrile panniculitis is obscure and that studies in this field are badly needed. Leucopenia seems to be a frequent manifestation of the disease, and a remarkable recent finding has been the presence of cryoglobulins in the plasma. This finding was confirmed in the case of our patient. I believe that it is not of basic significance and that some nodules suppurate and some do not. All lesions are inflammatory, and probably they progress to suppuration according to the severity of the inflammatory process.

Among the many underlying causes of erythema nodosum, brucellosis should be mentioned. In this infection severe attacks of erythema nodosum occur and recur with febrile flare-ups of the systemic disease.

Pemphigus Vulgaris in a Girl Aged 15 Years. Presented by DR. A. M. BUCHHOLZ and (by invitation) DR. M. P. LAZAR.

DISCUSSION

DR. STEPHEN ROTHMAN: It is conspicuous how much corticotropin or cortisone can be tolerated by pemphigus patients without their developing signs of hypercorticoidism. One may speculate that in pemphigus there is an adrenocortical insufficiency to start with, as it was indicated by the work of Lever. Certainly in pemphigus the tolerance is much better than in other diseases.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: There is one drawback to the long-continued administration of steroids in the elderly, and that is the development of osteoporosis secondary to a loss of proteins. When such a program of treatment is planned in the case of patients with pemphigus, for example, it may be well to have an x-ray of the spine made early in the course of the disease to establish a baseline for purposes of comparison.

I do not think the development of osteoporosis is purely a matter of steroid dosage. I have seen it on two occasions in older patients with pemphigus, in one of whom collapse of two vertebrae occurred suddenly and without warning. This patient was an elderly man who had been on moderate doses of cortisone intermittently for two years with fairly good control of the pemphigus until the final few weeks of his illness.

DR. THEODORE CORNBLEET: It has been suggested that testosterone overcomes the osteoporosis from the use of steroids. I have had no chance to verify.

Sarcoid. Presented by DR. JOHN C. SLAUGHTER, JR., Evansville, Ind.

DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I think the diagnosis of sarcoidosis is correct in this most interesting case of Dr. Slaughter's. I do not know whether the stumbling that the mother mentions is part of the condition or not, but intracranial lesions are quite often reported, and the symptoms of brain tumor have been reported quite a number of times.

Coccidioidomycosis with Cutaneous Involvement. Presented by DR. EDWARD A. OLIVER and staff.

History.—J. R. Y., a 34-year-old Negro man, was stationed in southern California while in the services approximately 10 years ago. About three years ago he developed redness, swelling, and pain associated with a small amount of discharge from the left index finger, said to have followed an injury and persisting until the present time. About one year ago he developed a small

coin-sized, oval lesion on the bridge of the nose. About four months ago he began to complain of a moderate productive cough followed in some two months by wheezing, dysphagia, and weight loss of 15 to 20 lb. (6.8 to 9 kg.).

Physical Examination.—Examination revealed redness, swelling, nail dystrophy, and multiple small erosions of the terminal phalanx of the index finger, left hand, as well as a small, coin-sized, oval, crusted lesion of the bridge of the nose. Examination of the larynx revealed considerable edema of the arytenoids and of the upper glottic folds, with ulceration on the laryngeal surface, and in the interarytenoidal areas extending into the ventricles a fungating, grayish-white mass was seen.

Laboratory Findings.—Positive findings included a bilateral annular mass which occluded the larynx on a laminogram. Urinalysis revealed a trace of albumin and 25 white cells per high-power field. Total protein 8.8 gm. per 100 cc., with 2.5 gm. albumin and 6.3 gm. globulin.

Biopsy and culture of both cutaneous lesions revealed refractile bodies suggestive of Coccidioides immitis, while culture verified this. Chest x-ray was negative. X-ray of the left index finger revealed small localized areas of erosions. Skin tests were returned as positive for first strength PPD and negative for histoplasmin, blastomycin, and coccidioidin.

Shortly after admission a tracheotomy was performed, and at the time of surgery biopsy of the lesion was positive for Coccidioides immitis. For the past month the patient has received 150 mg. of 2-hydroxystilbamidine in 200 cc. of saline I. V. daily.

DISCUSSION

DR. STEPHEN ROTHMAN: Is it not rather unusual to have a negative coccidioidin test in a case with active lesions?

DR. E. A. OLIVER: As you all know, this disease is quite commonly seen in California, especially in the San Joaquin Valley. This young man comes from California. I cannot explain the negative test, but the organism was found and the microscopic sections were diagnostic. The pathologist at the Veterans Hospital made the diagnosis.

These cases are seldom seen here in Chicago. Blastomycosis is common in the Middle West and coccidioidomycosis is common in California.

Adenoma Sebaceum Presented by DR. FRANCIS E. SENEAR and (by invitation) DR. DAVID W. KERSTING.

History.—Since the age of 3 years, N. G. V., a 9-year-old white girl, an only child, has progressively developed red and yellowish macules and papules on the face, neck, and suprasternal area. At the onset a single lesion usually appears as a tiny red punctum which enlarges and becomes papular. Some fuse with neighboring lesions to form irregular tan-colored plaques.

The child had recurrent convulsions beginning at the age of 4 months, these occurring about once or twice monthly and ending at the age of 18 months. When she was about 5 years of age, she began to have psychomotor seizures. These have greatly lessened in frequency since trimethadione (Tridione), phenobarbital, and triple bromides have been used prophylactically. Her mental development appears to have been normal. The neurological examination is negative except for extremely hyperactive deep tendon reflex responses in the lower extremities. No retinopathy was found. There is no family history of convulsive disorders or skin disease.

Physical Examination.—The lesions on the face are bilaterally symmetrical and tend to be placed centrally. For the most part they consist of discrete, red papules mixed with an occasional nevus-araneus-like macule. On the forehead, left side of the neck, and suprasternal region there are soft, yellow-brown, irregular, flat plaques. An elevated, vascular papule, measuring 3 by 3 by 3 mm., which formed in the left nasolabial fissure, has developed a filiform verrucous summit. This lesion has been destroyed twice by actual cautery, but has recurred each time. A biopsy specimen secured on the last occasion is presented.

Laboratory Findings.—The urinalysis, hemoglobin, and total and differential blood leucocyte counts have been normal.

The electroencephalogram was interpreted as showing psychomotor foci with slowing in the left anterior temporal and left midtemporal regions with a few suggestive discharges in the right anterior temporal region.

The skull x-ray film revealed small intracranial calcifications lying in cortical and subcortical areas.

Pathologic Report.—Grossly the tissue consisted of a small rounded hemisphere of soft yellowish-red tissue with a verrucous surface. Microscopically the epithelium was acanthotic and hyperkeratotic, with areas of parakeratosis and an increase in amount of cells of the granular layer. The papillary corium was quite vascular, and the reticular corium was moderately fibrotic and permeated with numerous ectatic and dilated blood vessels.

DISCUSSION

DR. DAVID W. KERSTING (by invitation): It is my impression that if adenoma sebaceum as a name for this condition is not a misnomer, it is at least misleading. As Dr. Ebert pointed out, the patient here has Bourneville's disease or epiloia, a congenital syndrome characterized by epilepsy, intracerebral sclerotic glial tumors, and mental deficiency. Certainly the condition was recognized long before Balzar in 1885 and Pringle in 1890 attached the term "adenoma sebaceum" to the skin lesions which they observed as a frequent concomitant symptom. The dermal lesions are usually hamartomas—overgrowths of vascular and connective tissue, less frequently "adenoma sebaceum." This poor term is not to be confused with senile sebaceous hyperplasia, or true sebaceous adenoma, or nevus sebaceus. Recently I had an opportunity to study the dermal lesions in a significant number of cases of epiloia and found abnormality of sebaceous tissue most infrequently.

The essential histologic features of the disease are hard intracerebral gliomas, retinal neuroglial phakomas, dermal hamartomas of connective and vascular tissue, renal tumors, cardiac rhabdomyomas, and tumors in other organs, but the intracranial lesions, which in our case appear to have calcified, probably produce the characteristic symptoms and are predominantly responsible for the generally poor prognosis of these unfortunate children.

Cholinergic Urticaria? Presented by DR. STEPHEN ROTHMAN.

History.—T. McD., a 26-year-old white medical student, was first seen at the University of Chicago Clinics on March 12, 1954. Since the age of 13 he has developed a red, itching skin eruption following excitement, physical exercise, and sudden exposure to warm temperatures. The eruption usually involves the face, most of the trunk, and at times an extremity. Pruritic confluent hives and giant edema are said to develop. Single lesions persist for about 45 minutes. There was one episode of laryngeal edema. Mydriasis of several hours duration allegedly also develops.

Exercise in a warm room resulted in the development of a macular erythematous eruption over the face, neck, and shoulders.

Laboratory Findings.—Acetylcholine 1:100,000 intradermally gave no reaction, but 1:10,000 produced an area of erythema 2.5 cm. by 1.0 cm. and a wheal 1.0 cm. in diameter.

DISCUSSION

DR. I. M. FELSHER: An interesting point was brought out by the patient himself. He stated that if he exercised energetically in the morning he usually did not develop any lesions during that day. He also noticed that he never developed any lesions on the forehead, palms, or soles, the common freely sweating areas. Evidently there is some relationship of the urticaria to the sweat apparatus.

Hyperkeratosis Palmaris et Plantaris. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. LEONARD HOIT.

Lichen Sclerosus et Atrophicus—Morphea? Presented by DR. J. WEBSTER and S. HUFF, and (by invitation) DR. H. MARKS and DR. J. SICKLEY.

Pituitary Dwarfism with Scleroderma? Presented by DR. S. BLUEFARB and DR. H. RODIN, and (by invitation) DR. LEONARD HOIT.

Vitiligo. Presented by DR. THEODORE CORNBLEET and DR. SIDNEY BARSKY, and (by invitation) DR. HAROLD MARKS.

Hyperpigmentation. Presented by DR. IRENE NEUHAUSER and (by invitation) DR. S. WILLIAM BECKER, JR.

Pigmented Eyelids? Case for Diagnosis. Presented by DR. L. F. WEBER and DR. IRENE NEUHAUSER.

Ocular Pemphigus? Erythema Multiforme? Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. HAROLD MARKS.

Pityriasis Rubra Pilaris? Presented (by invitation) by Dr. Allan L. Lorincz and Dr. Edward H. Ferguson.

Rhinophyma Excised with the Cutting Current. Presented by Dr. Robert M. Goodwin, Springfield (by invitation).

Rosacea with Rhinophyma and Persistent Edema. Presented by Dr. Edward A. Oliver and staff.

Case for Diagnosis: Leukoplakia and Psoriasis; Lichen Planus? Presented by Dr. Otto C. Stegmaier.

Radiodermatitis. Presented by Dr. A. M. Buchholz and (by invitation) Dr. M. P. Lazar.

THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

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Feb. 23, 1954

Vitiligo Associated with Poliosis and Ichthyosis. Presented by Dr. Margaret Ann Storkan and Dr. John A. Hosmer (by invitation).

B. R., an 8-year-old white boy of English descent, has had "white spots of the skin" and hair color changes since birth. The area of scaling, and dryness of his arm was noted several years ago. The general history is noncontributory.

Examination shows the boy is well developed and well nourished and has marked areas of depigmentation, of varied size and shape, on his trunk and arms. He has also a white forelock.

The skin depigmentation has been present in the paternal family for over 200 years. It seems to follow a dominant trait tendency. It was recalled that similar areas have been observed in different members of the family. The white forelock also is predominant.

The specimen for biopsy was removed from the ichthyotic plaque of his arm.

DISCUSSION

Dr. Margaret Ann Storkan (Comments—Slide): The microscopic picture is consistent with that of an ichthyosis simplex.

Dr. Meyer Berke: In view of the congenital and familial history of patches of depigmentation and poliosis in this patient, the use of the term vitiligo is incorrect, and more properly the condition should be called partial albinism.

Dr. John W. Carney: I doubt very much if we can change a condition that has been familial for 200 years; however I think the child should have the benefit of at least a trial attempt to improve the depigmentation. There would be few advances in dermatology if we always threw up our hands saying that "such and such a condition," as far as treatment is concerned, is hopeless. Of course with this child the parents would have to understand that we are attempting under the circumstances to do the best that we can. I would suggest a trial of ammoidin (Ammi majus Linn.) locally and orally. My experience with ammoidin, so far, is that the results from its use are unpredictable. Sometimes bullae, inflammatory reactions, and hyperpigmentation occur and other times they do not. If toxic reactions from using ammoidin orally are feared, then a solution of the substance could be applied locally and followed by ultraviolet irradiation. On the whole with this medication the local reactions that I have seen have not been any more severe than those resulting from the many other irritants that at times have been used in the treatment of vitiligo.

Dr. Fred F. Feldman: Have you found a spotty hyperpigementation after using ammoidin?

Dr. John W. Carney: Yes, a spotty pigmentation frequently occurs as one of the end results but over a period of time (weeks to months) a gradual blending of hyperpigmented islets will be seen.

Dr. Leonard E. Savitt: The first instance in which I used psoralens in vitiligo orally and locally resulted in a good clinical response with no toxic symptoms. The second patient on whom I used psoralens orally and locally had a toxic reaction consisting of nausea, vertigo and asthenia of such severity that he was unable to work for two weeks. Since then I have not used the preparation orally. Two dermatologists have reported to me rather severe bullous reactions due to the local use of psoralens.

I have been using psoralens (Biomoidin solution: Bioproducts) locally to produce erythema in alopecia areata. The results have been at least as successful as with phenol followed by alcohol and have been less irritating.

DR. MAX POPPER: There are a number of reports in the literature of the familial incidence of vitiligo. I recently had the opportunity to observe two sisters with this condition. The lesions in both patients occurred on identical sites. Gougerot reports a similar case in a brother and sister (Bull. Soc. franç. dermat. et syph. **25**:334, 1914-1915).

Vitiligo is not due to the absence of melanocytes. It has been demonstrated that the vitiliginous skin contains as many melanocytes as the normal skin (Becker, S. W., Jr.; Fitzpatrick, T. B., and Montgomery, H.: Human Melanogenesis: Cytology of Human Pigment Cells, A. M. A. ARCH. DERMAT. & SYPH. **65**:511, 1952). Although the pathogenesis of vitiligo is not yet well understood, it is thought to be based on an inability of the melanocytes to convert tyrosine into melanin. This inability of the melanocytes takes place only in later life after years of normal activity of these cells, suggesting that in areas which will develop vitiligo these cells can maintain their function only for a restricted period of time. It is probable that this peculiarity of the melanocytes is due to a genetic factor.

DR. STANTON B. MAY: Is this picture anything similar to what we call Vogt-Koyanagi syndrome.

DR. EDWARD MURPHY: I agree with Dr. Berke. I believe that the symmetry of these lesions derives from heredity. This congenital epidermal defect is quite apart from the ordinary vitiligo. However, I believe this patient should be treated with psoralen. I have treated three cases of vitiligo with psoralen; one in a child about 8 years old, one in a man about 25, and one in a man around 48. The child cleared probably 90%; the man around 25 cleared possibly 75%, and the older man has cleared about 25%. He is still under treatment after one year. On each one of these patients, I used local liquid psoralen on one side and not on the other for a period of about six weeks on the average, with no benefit. I am loathe to accept the local application of the drug in this disorder. On the other hand, I believe the product orally does have some benefit. I found no toxic reaction in any of these cases.

DR. CHARLES SHERTER: In agreement with Dr. May, I think one should consider the Vogt-Koyanagi syndrome in this patient despite the fact that all the classical signs and symptoms are not present.

However, from a therapeutic standpoint little is accomplished by appending a specific name to the disease except for academic interest.

DR. MARGARET ANN STORKAN: Thank you for the discussion and especially the nosological differentiation from Dr. Berke. This is my first opportunity to see in a child the syndrome of familial albinism, poliosis, and ichthyosis simplex.

Probable Lymphoblastoma (Mycosis Fungoides). Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Colloid Degeneration of the Skin; Colloid Milium? Presented by DR. EDWARD L. MURPHY.

Case Presented for Diagnostic and Therapeutic Suggestions. Presented by DR. LAURENCE J. UNDERWOOD and DR. WALTER S. GREEN.

Acrosclerosis with Raynaud's Phenomena. Presented by DR. STANTON B. MAY for discussion of therapy.

Prurigo Nodularis vs. Excoriation. Presented by DR. MURRAY ZIMMERMAN.

Perifolliculitis Capitis Abscidens et Suffodiens, Limited to Sideburns Areas vs. Deep Fungus Infection. Presented by DR. MURRAY ZIMMERMAN.

Nevus Flammeus. Presented by DR. STANTON B. MAY for therapeutic suggestions.

Case for Diagnosis. Presented by DR. MEYER BERKE.

PHILADELPHIA DERMATOLOGICAL SOCIETY

Bertram Shaffer, M.D., *Chairman*

Lewis M. Johnson, M.D., *Secretary*

Jan. 15, 1954

Multiple Basal Cell Epithelioma and Other Conditions. Presented by DR. MARJORY K. HARDY and (by invitation) DR. JORGE PAREDES.

H. M., a Negro man aged 41 years, presented over the right side of the scalp and on the upper lip large, rather well demonstrated areas characterized by groups of papules and plaques

with many contained comedones. Scattered about in these plaques and on the other side of the scalp, as well, are numerous blue-black, pigmented macules and papules. Several small, atrophic defects were present on the nose, and numerous seborrheic keratoses and pigmented skin tags over the rest of the body.

The report on the biopsy specimen on June 8, 1953, was basal cell epithelioma; on June 18, 1953, basal cell epitheliomata. On Oct. 30, 1953, the report was as follows: Papillomatous hyperplasia, hyperkeratosis, acanthosis and focal parakeratosis. In some areas there was vacuolization of the upper rete Malpighii and granular layer. On Dec. 7, 1953, it was reported as basal cell epithelioma. All the slides were reviewed by Dr. Herman Beerman and reported as basal cell epithelioma.

One large nevoid lesion on the scalp was excised.

DISCUSSION

DR. ALBERT M. KLIGMAN: This patient has more than basal cell carcinoma. In fact, he shows the whole spectrum of organoid or adnexal tumors, as well as epidermal proliferation of the epithelial nevus type. The changes range from a simple nevoid condition to a complete dedifferentiation into unorganized epithelial masses. I believe that this case is instructive because it throws light on the origin and development of adnexal tumors. Conflicting attitudes can be resolved by assuming that an epithelial cell, whether on the epidermis or in the adnexa, has pluripotential characteristics; it can form cells which differentiate toward hair, sebaceous glands, or apocrine glands. Epithelial nevi represent simple overgrowth of normal tissue. The stimulus that causes epithelial hyperplasia and differentiation is, of course, unknown, but this patient illustrates the entire gamut of changes when epithelial cells are released from their normal control.

DR. BERTRAM SHAFFER: I, too, think this is quite obviously a nevoid process in which some of the lesions have taken on the histologic characteristics of true basal cell epitheliomas. There have been reports of true basal cell epitheliomas arising from multiple benign cystic epitheliomas. Presumably this represents a spectrum of changes even wider. Some of the lesions look like adenoma sebaceum. There were some shagreen patches on the lip which fit in with this picture.

DR. JOHN H. YEAMANS (by invitation): I took three or four biopsy specimens from the scalp, and they were all basal cell epitheliomas.

DR. MEYER L. NIEDELMAN: Were any of the biopsied lesions pigmented, deep blue, resembling comedones?

DR. JOHN H. YEAMANS (by invitation): There was much pigment in these tissues: melanin.

DR. MEYER L. NIEDELMAN: I believe that any precancerous or cancerous lesion should be eradicated, irrespective of where it is located. The type and extent of treatment would depend on many factors. Although the present lesions are slow-growing, they are already cancerous, and electrocoagulation would be the best method.

DR. ALBERT M. KLIGMAN: The pathologic report does not harmonize with clinical observation. We should not allow the focal vision of the pathologist, who has only a sectional view of the matter, to formulate without qualification a diagnosis which, if accepted, would commit us immediately to a destructive form of therapy. These are not basal cell carcinomas clinically. The patient has lived with these lesions for years, and they have not exhibited "rodent" qualities.

DR. JOHN F. WILSON: I accept the diagnosis of basal cell epitheliomata, but this patient's lesions are very slowly progressive. I would not treat any of these lesions at the present time. I would observe the patient, but in view of the status of his mentality, I doubt that one would get very good cooperation from him either for complete treatment or even further observation. Even at the risk of poor follow-up, I would watch him carefully to see what happened with the lesions before I would treat any of them.

DR. A. STRAUSS: I agree with that.

Kaposi's Sarcoma with Atrophy of Toes.(?) Presented by DR. CARMEN C. THOMAS. and (by invitation) DR. DONALD MADDEN.

Multiple Hidrocystoma(?) Presented by DR. MARJORY K. HARDY and (by invitation) DR. JORGE PAREDES.

Fox-Fordyce Disease. Presented by DR. BENJAMIN GROSS and (by invitation) DR. EDWARD KARAMANOUKIAN.

Scrofuloderma. Presented by Dr. Carmen C. Thomas and (by invitation) Dr. Donald Madden.

Chronic Discoid Lupus Erythematosus? Hypertensive Cardiovascular Disease. Presented by Dr. Carmen C. Thomas and (by invitation) Dr. Donald Madden.

Rheumatoid Nodules. Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Jorge Paredes.

Sulzberger-Garbe Syndrome. Presented by Dr. Benjamin A. Gross and (by invitation) Dr. Edward Karamanoukian.

Healed Scars of Treated Tertiary Syphilis. Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Edward Karamanoukian.

Chronic Discoid Lupus Erythematosus. Presented by Dr. Carmen C. Thomas and (by invitation) Dr. Donald Madden.

Granuloma Inguinale. Presented by Dr. Carmen C. Thomas and (by invitation) Dr. Donald Madden.

Poikiloderma Atrophicans Vasculare? Lymphoblastoma? Parapsoriasis? Presented by Dr. Benjamin A. Gross and (by invitation) Dr. Jorge Paredes.

Drug Eruption? Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Edward Karamanoukian.

THE RHODE ISLAND DERMATOLOGICAL SOCIETY

Carl D. Sawyer, M.D., *President*

Malcolm Winkler, M.D., *Secretary*

Jan. 20, 1954

Cavernous Hemangioma: Spontaneous Involution. Presented by Dr. Bencel L. Schiff, Pawtucket.

A 7-weeks-old girl was seen on June 26, 1952, with a cavernous hemangioma, involving the left upper eyelid, eyebrow, and forehead. The eye could barely be opened, and a discharge was noted. The parents consented to expectant therapy. On March 20, 1953, the child was reexamined, and part of the lesion of the forehead had undergone involution. Patient was again seen

(Left)—Hemangioma at age of 7 weeks, June 26, 1952. (Right)—The same, March 9, 1954. No treatment of any kind.

on March 9, 1954, 21 months after the first examination, and complete disappearance of the lesion from the forehead, eyelid, and eyebrow was noted. The child was able to open the eye almost normally.

DISCUSSION

Dr. Malcolm Winkler, Providence: We are all familiar with spontaneous involution of hemangioma. There are cases in which treatment can wait, but it is questionable whether it is advisable to wait in all cases.

Dr. Carl S. Sawyer, Providence: Was there any evidence of inflammation?

Dr. Bencel L. Schiff, Pawtucket: It showed no inflammation whatever. I became interested in the subject of spontaneous involution of vascular tumors after hearing a paper by Dr. Ronchese at the International Congress in London, in 1952 (Ronchese, F.: The Spontaneous Involution of Cutaneous Vascular Tumors, *Am. J. Surg.* **86**:376 [Oct.] 1953). If the heman-

gioma is located on the face it is difficult to persuade the parent to wait. Another case I have observed involved a 7 months' old baby with a strawberry mark on the cheek. It took three and one-half months to disappear. Bleaching begins in the center, and progresses towards the periphery. There is no way to know beforehand which hemangioma will disappear spontaneously and which will not. At any rate, there is no harm to wait for at least six months.

DR. VINCENT J. RYAN, Providence: It has been my observation for years that the so-called cavernous hemangiomas do disappear without treatment. I am interested in Dr. Schiff's report about the strawberry type clearing without treatment. I have seen the vascular type of lesions disappear. There is no question that most lesions disappear before the child reaches puberty.

DR. FRANCESCO RONCHESE, Providence: This is certainly a good example of spontaneous involution of a bad case of hemangioma, a case which should present a problem for any specialist. Strangely enough, the location of the hemangioma seems to have something to do with a spontaneous involution, just as in cases of alopecia areata, in which certain areas of the scalp are slower than others in filling in. I have seen two other cases and read of two others, all horribly involving an orbital area like the one presented by Dr. Schiff. They had the same dreadful appearance and presented the usual difficult therapeutic problem. They all cleared without treatment of any kind.

Lupus Erythematosus, Chronic Discoid. Presented by DR. FRANCESCO RONCHESE, Providence.

Dermatitis Medicamentosa. Presented by DR. VINCENT J. RYAN, Providence.

Hairy Tongue. Presented by DR. FRANCESCO RONCHESE, Providence.

Lupus Erythematosus Chronic Discoid with a Herpes Zoster Distribution. Presented by DR. FRANCESCO RONCHESE, Providence.

Dermatitis Medicamentosa. Presented by DR. VINCENT J. RYAN, Providence.

Lichen Nitidus. Presented by DR. VINCENT J. RYAN, Providence.

Erythema Multiforme Bullosum on a Psychosomatic Base. Presented by DR. FRANCESCO RONCHESE, Providence.

Dermatitis Medicamentosa. Presented by DR. VINCENT J. RYAN, Providence.

Hydroa Aestivale. Presented by DR. MALCOLM WINKLER, Providence.

Dermatitis Herpetiformis. Presented by DR. WILLIAM B. COHEN, Providence.

Vitiligo. Presented by DR. BENCEL L. SCHIFF, Pawtucket.

Unilateral Melanoderma. Presented by DR. MALCOLM WINKLER, Providence.

Obituaries

OLIVER S. ORMSBY, M.D.
1874-1954

OLIVER SAMUEL ORMSBY died of pneumonia at his home in Glencoe, Ill., April 9, 1954. His death ended the career of one of the most distinguished dermatologists of the past fifty years.

Dr. Ormsby was born in Logan, Utah, March 21, 1874, and graduated from Rush Medical College in 1895. After graduation he returned to Utah, where he engaged in general practice for several years. He then became associated with Dr. James Nevins Hyde and Dr. Frank Hugh Montgomery in Chicago. In 1913 Dr. Ormsby was made Professor and Head of the Department of Skin and Venereal Disease at Rush. After the affiliation of Rush Medical College with the University of Illinois, he was Clinical Professor (Rush) and continued in that capacity and also as Chairman of the Department of Dermatology at the Presbyterian Hospital until he became Professor Emeritus in 1942.

In 1901 he went to London to study dermatology, and while there he and MacLeod demonstrated for the first time tubercle bacilli in a patient who had tuberculids. It was during his stay in London that the Chicago Dermatological Society was organized, and, although he was not present at the organizational meeting, he was voted into the Society as a charter member, and he remained an enthusiastic and regular attendant at the meetings until his last illness. His participation in the activities of the Chicago Dermatological Society is indicated by the fact that he was President in 1911, again in 1933, and in 1952 was elected Honorary President.

In 1908 he became a member of the American Dermatological Association, and he served as Secretary from 1914 to 1920; Vice-President in 1920-1921; and President in 1921-1922. He was wholeheartedly devoted to the American Dermatological Association and held a record of almost perfect attendance at the meetings. For many years he was Chairman of the Membership Committee, a position he felt carried with it great responsibility, and one that he worked at diligently.

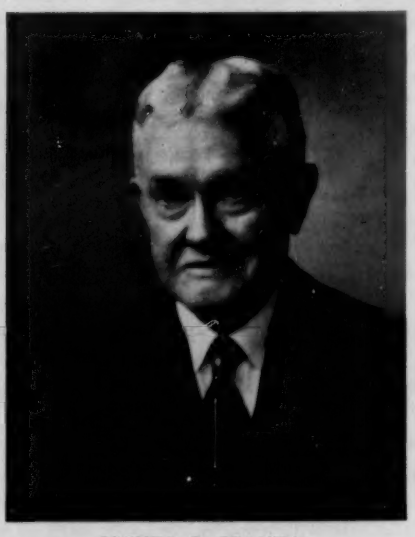
Dr. Ormsby was much interested in blastomycosis and contributed many papers on the subject, either alone or in collaboration. He was also interested in the differential diagnosis and etiology of lichen sclerosis et atrophicus, morphea, and white-spot disease.

In 1914 he assumed the editorial preparation of "The Year Book of Skin and Venereal Diseases," an undertaking on which I collaborated and which continued for some years.

In 1915, Dr. Ormsby's extensive revision of the Hyde and Montgomery text, "Practical Treatise on Diseases of the Skin," appeared. Dr. Ormsby's book has gone through seven editions, and the eighth revision is now in press. It still remains one of the outstanding dermatological textbooks. Dr. Hamilton Montgomery, son of one of the original authors, collaborated in the sixth and seventh editions in 1943 and 1948, and will continue as the author.

At the Annual Meeting of the American Medical Association in Detroit in 1916, the first comprehensive paper on "Ringworm of the Hands and Feet" was presented by Ormsby and Mitchell. Prior to this presentation only seven similar cases had been reported in this country.

As a clinician, Dr. Ormsby was truly great. He had an uncanny gift for diagnosis and therapy; in many years of association with him I know of no one who surpassed him and few who could be classed as his equal. As a teacher he was famous. The students at Rush Medical College clamored to attend his clinics and those who were not accepted because of the limitation of numbers nevertheless visited his clinics frequently and continued to do so again and again while in residence.



OLIVER S. ORMSBY
1874-1954

Dr. Ormsby was the recipient of many well-deserved honors. He was Chairman of the Section on Dermatology and Syphilology of the American Medical Association, 1919-1920; President of the Institute of Medicine of Chicago, 1940; President of the Tenth International Congress of Dermatology, which was postponed because of World War II. In 1951, he was elected an honorary member of the American Dermatological Association. He was also an honorary member of the following societies: Manhattan Dermatological Society; Minnesota Dermatological Society; Section on Dermatology, Royal Society of Medicine, London; The Dutch Society of Dermatology; Deutsche Dermatologische Gesellschaft, Munich; Asociatión Argentina de Dermatologia y Sifiología, Buenos Aires; Wiener Dermatologische Gesellschaft, Vienna; Japanese Dermatological Society, Tokyo; Greek Union of Dermatology and Venereology, and Hellenic Antivenereal Society, Athens. He was a Corresponding Member of the Société Française de Dermatologie et de Syphiligraphie, Paris; Swedish Dermatological Society, and Dansk Dermatologisk

Selskab, Copenhagen. He was a member of the Congress of American Physicians and Surgeons; American Academy of Dermatology and Syphilology, and the Chicago Pathological Society.

Dr. Ormsby was a punctual and meticulous person, and because he was an expert and exacting teacher he exerted a great influence on American dermatology. He took great pride in his work, especially in his teaching, his office, and his book. As a master clinician, he had the ability to describe dermatoses vividly and accurately. In recent years his attendance at dermatological society meetings lent dignity to the occasion, and, as he was a retiring type, somewhat difficult to know intimately and not given to levity or frivolity, by his presence the discussions were kept restrained, formal, and impersonal. For a number of years Dr. Ormsby had an obscure pulmonary condition which limited his activities but did not greatly curtail them, and up until his last illness he was an enthusiastic and serious golfer, as well as an equestrian.

Dr. Ormsby is survived by his second wife, Mary Horton Ormsby; a daughter, Miriam (Mrs. Cyrus Mark), and a grandson, Ormsby Annan; and by a large number of dermatologists whom he trained and who have become leaders and teachers of American dermatology. With his death the dermatologic office started by Dr. Hyde in 1873, and maintained constantly since then, has closed for the last time. An era in dermatology typified by men who pioneered in the field of cutaneous diseases, who did not have the opportunity for formal training in recognized and approved schools, comes to a close with his passing. Men of this type will live long in our memory.

JAMES HERBERT MITCHELL, M.D.

News and Comment

ANNOUNCEMENTS

Continuation Course in Dermatology, University of Minnesota.—The University of Minnesota announces a continuation course in dermatology for specialists which will be held at the Center for Continuation Study on the University campus next Oct. 28 to 30, 1954. The program will deal with many topics of current interest to practicing dermatologists; sarcoidosis will receive special emphasis. The program will be presented under the direction of Dr. Henry E. Michelson, Professor, Department of Medicine, and Director, Division of Dermatology, University of Minnesota. Lodging and meal accomodations are available at the Center for Continuation Study.

Books

You and Your Skin. By Norman R. Goldsmith, M.D. Price, $3.75. Pp. 148. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

The blurb on the jacket calls this "an unusually readable account of what your skin is like. . . ." It states that "physicians may wish to keep four or five copies in their office and keep them in circulation among patients under their care." This reviewer, for one, would not consider exposing his patients to a book so full of flaws.

The grammar is below the minimum standard; sentences are often incomplete; tenses are changed haphazardly; pronouns lack proper antecedents; misspellings are so flagrant that one is at first inclined to accuse the printer, until recurrence makes it clear that the fault is the author's ("bazaar" instead of "bizarre"; "madamoiselle" for mademoiselle"; "Levadite" instead of "Levaditi"). The choice of words in many instances is confusing, if not suggestive of illiteracy, e. g., "a sulfa-contained ointment," the use of "intervene" when "supervene" is meant, the advice to "consult expert advise," and "pediculosis corporis lay eggs in the seams of clothing."

There is endless repetition in both the choice of words and the stating of facts. It is at times hard to decide whether the construction is a feeble attempt at humor or merely a feeble attempt to compose a sentence. Obvious attempts at humor outrage good taste in many instances, and are always labored, as in such statements as the following: "They [the apocrine glands] secrete fatty substance which produces the scent that makes boy want to meet girl." "Animals have claws, but women use nail polish. Both may cause damage." "But, if your dog or your husband chased you, what should you do?"

The "unique chapter titles" mentioned in the blurb are indeed unique: "Grapes of Wrath" takes this appellation from the fact that stained staphylococci look like clusters of purple grapes. Under "Nerves—the Fifth Column" it is noted that "skin diseases are unique in that, except for those caused by any of the attackers discussed thus far, man is the only animal which develops a neurodermatosis. Your dog may howl or be unhappy but he does not develop a skin lesion thereby." The chapter title "Hair—Your Biggest Headache" is elaborated in the text as follows: "Basically, hair is civilization's biggest headache." A discussion of tularemia, under the subtitle "Rabbit Bites Man," starts with the sentence, "The little bunny, which the hunter so blithely marches forth and blasts, gets his revenge."

Factual errors and unsupported statements abound: In reference to "winter itch" it is said that "In the aged and those with abnormally dry skin, an increase in the amount of fats eaten may help." According to this book, "Petroleum products, like petrolatum . . . actually defat the skin," "Among commonest sites [of fungous infection] are . . . inside the ears," and "If the skin of a patient is stroked the papules [of lichen planus] will often follow the line. This is known as Wickham's striae." The source consulted for the chapter on syphilis must have had a publishing date of about 20 years ago because the figures cited appear correct for that period: "In the United States, there are about 500,000 new cases of syphilis each year."

This book does not warrant so lengthy a review, but its release by a publishing house that purports to specialize in the fields of medicine, science, and technology raises an important question: It would seem that such a publisher has an obligation to those fields of science from which he derives the material on which his business depends, an obligation to evaluate a manuscript before handing it over to the printer. Such an evaluation would be expected to include at least a minimum standard of grammar as well as the advice of a consultant in the field of science concerned as to the accuracy and suitability of its content for lay consumption. In the case of "You and Your Skin" the publisher's staff from the executive level down to the copy reader were evidently asleep.

Histopathologic Technic and Practical Histochemistry. By R. D. Lillie, M.D. Price, $7.50. Pp. 501. Blakiston Company, 575 Madison Ave., New York 22, 1954.

This edition was preceded in 1947 by one entitled "Histopathologic Technic." The author in the present edition has endeavored to include selected variants of the newer methods, especially histochemical procedures. He states that he has emended these procedures and methods so that they may be followed without personal instruction. He emphasizes the importance of optimal times, temperatures, pH levels, and reagent concentrations in demonstrating certain constituents of the skin or other organs of the body. The first 128 pages are devoted to concise and instructive recommendations in the care and use of the microscope, laboratory equipment, and the process of fixation, sectioning, stains, and mounting of tissues. The main portion of the book is devoted to techniques for the demonstration of various anatomical and chemical constituents of the tissues and accompanied by brief but adequate references in the text. The book is written in a narrative and easily legible form. It should prove to be of value not only to students wishing to learn histopathological and histochemical techniques but as a guide and source of reference to the more experienced research workers in these fields.

Physiology and Biochemistry of the Skin. By Stephen Rothman, M.D. Price, $19.50. Pp. 741, with illustrations. The University of Chicago Press, 5750 Ellis Ave., Chicago 37, 1954.

Rothman and his contributors in their book on physiology and biochemistry of the skin have brought together in one volume of over 700 pages all the important work both old and new on these subjects. These studies include extensive research done by Rothman in this field during the past 25 years. There are special chapters contributed by former students who are now members of his staff at the University of Chicago, namely, Dr. G. C. Wells and Dr. A. Lorincz. Contributions were also made by Dr. Z. Felsher and Dr. P. Flesch, as well as chapters on enzymes by Dr. A. B. Lerner, and on the biology of the epidermal cells by Dr. H. Pinkus. At the end of each chapter there is a pertinent and extensive bibliography arranged both alphabetically and by number. References are given to important contributions written in biochemical periodicals, as well as those to be found in journals on dermatology and various phases of clinical medicine as a whole. The foreign literature on the subject is thoroughly covered. The presence of a table of contents at the beginning of each chapter, together with the many references and the complete subject and author index, make this an extremely valuable reference book, and this arrangement results in a book that is relatively easy to read for one on such a complex subject.

The author presents concisely and clearly various controversial points of view. The rapid development of physiology and biochemistry of the skin within the last 20 years is evident after reading this book. At the same time it is noted that there are many problems that have only

been touched on and many others that remain to be solved. The illustrations, although not numerous, are all of excellent quality, and the format of the book, the paper and printing are to be commended.

Rothman's book clearly brings out the importance and significance of physiologic and chemical studies in dermatology and also stresses the relationship of dermatology to internal medicine and systemic disease. The book is highly recommended to all dermatologists, especially those interested in research, and to all physiologists and medical chemists, and it should be available for reference to all physicians and research workers interested in any phase of physiology and biochemistry of the skin.

Dr. Rothman is to be congratulated for having compiled such a great fund of information, and for having spent a tremendous amount of time and effort to produce a book that will be for years to come the guide to investigators in skin physiology and chemistry.

CORRECTIONS

The correct address of Dr. Coleman Mopper, Secretary of the Detroit Dermatological Society, is 14633 E. Seven Mile Road, Detroit 5. Mail intended for the Society should be sent to this address.

J. A. Grant Peterkin's name was followed by M.D. on page 366 of the September issue of the ARCHIVES. The correct degrees are M.B.E., M.B., F.R.C.P. (Ed.).

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New and Nonofficial Remedies, 1953:48

Southern Medical Journal, January, 1951:42-44

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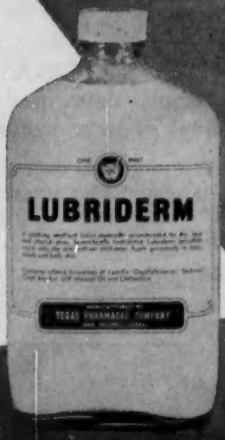

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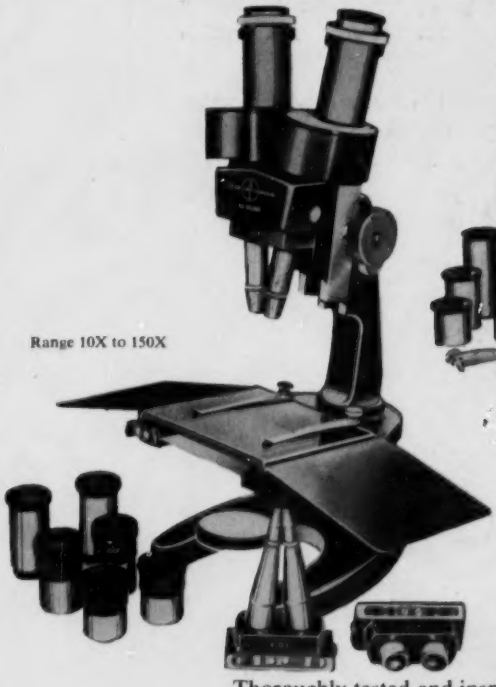

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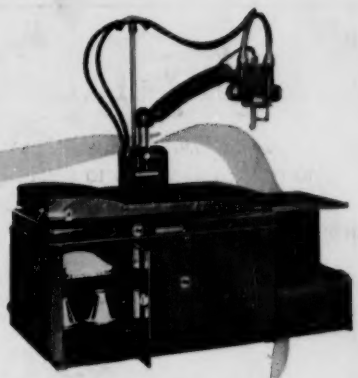

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